Handbook of Bleeding and Coagulation for Neurosurgery

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We dedicate this book to our wives and children in recognition of the hours stolen and to our patients who entrust us with their care.
# Contents

Foreword .................................................................................................................. xi
Preface ..................................................................................................................... xiii
Contributors ........................................................................................................... xv
Pharmaceuticals: Generic and Trademark Names ................................................. xix

## I Evidence-Based Medicine

1 The Role of Evidence-Based Medicine in Bleeding and Coagulation Management in the Neurosurgical Patient .................................................. 3
   Alexander A. Leung and William A. Ghali

## II Hemostasis and Coagulation

2 Coagulation and Platelet Plug Formation ............................................................ 17
   George M. Rodgers

3 Preoperative Coagulation Assessment for the Neurosurgical Patient ................. 26
   Venkatesh K. Rudrapatna and George M. Rodgers

4 Clinical Disorders of Coagulation and Platelet Function .................................. 38
   Justin D. Thomas and George M. Rodgers

5 Drugs Affecting Coagulation and Platelet Function .......................................... 47
   Amir Assel and Kenneth B. Hymes

6 Herbal Products and Supplements Affecting Coagulation ............................... 62
   Omar Tanweer, Shaun David Rodgers, and John G. Golfinos

## III Blood Loss and Replacement

7 Principles of Blood Loss ..................................................................................... 71
   Tsinsue Chen, Rami O. Almefty, and Peter Nakaji

8 Principles of Blood and Volume Replacement ..................................................... 85
   Rami O. Almefty, Tsinsue Chen, and Peter Nakaji

9 Blood Replacement .................................................................................................. 99
   Kenneth B. Hymes

## IV Management of Venous Thrombosis in Neurosurgical Conditions

10 Venous Thromboembolism (DVT and PE): Diagnosis and Treatment .......... 117
    Graham F. Pineo and Mark G. Hamilton

11 Venous Thromboembolism (DVT and PE): Prophylaxis ................................. 153
    Ryan Morton and Samuel R. Browd
12 Role of Anticoagulants in Common, Nonneurosurgical, Non-VTE Conditions
Christian A. Bowers and Robert C. Pendleton
............................................................................................................. 167

13 Cranial Venous Sinus Thrombosis Diagnosis and Management
Andrew Demchuk and Jose Andres Venegas-Torres
............................................................................................................. 184

V Management of Bleeding and Coagulation in the Neurosurgical Perioperative Period

14 Specific Anticoagulant and Antiplatelet Agent Reversal Strategies for Neurosurgical Patients
Shahid M. Nimjee and Gerald A. Grant
............................................................................................................. 199

15 Postoperative Strategies for Resumption of Anticoagulants and Antiplatelet Agents in Neurosurgical Patients
Douglas W. Sborov and George M. Rodgers
............................................................................................................. 208

16 Preoperative Non-Hematologic Adjuvant Methods for Preventing Blood Loss
Alejandro Santillan, Walter Zink, Lewis Leng, Shaun David Rodgers, and Howard A. Riina
............................................................................................................. 219

17 Intraoperative Non-Hematologic Adjuvant Methods for Preventing Blood Loss
Ian Y. Lee, Raymond Sawaya, and Nicholas B. Levine
............................................................................................................. 241

VI Management of Bleeding, Coagulation, and Venous Thrombosis in Specific Neurosurgical Conditions

18 Risk of Anticoagulants and Antiplatelet Agents in Brain Tumor Patients
David J. Daniels and Ian F. Parney
............................................................................................................. 259

19 Risk of Anticoagulants and Antiplatelet Agents in Common Neurovascular Conditions
Benjamin W.Y. Lo and R. Loch Macdonald
............................................................................................................. 269

20 Ischemic Stroke Diagnosis and Management
Michael D. Hill
............................................................................................................. 291

21 Neuroendovascular Issues
Alim P. Mitha, Michael K. Tso, Felipe C. Albuquerque, Cameron G. McDougall, and John H. Wong
............................................................................................................. 307

22 Neuroendovascular-Specific Patient/Case Examples
Alim P. Mitha, Michael K. Tso, Felipe C. Albuquerque, Cameron G. McDougall, and John H. Wong
............................................................................................................. 318

23 Risk of Anticoagulants and Antiplatelet Agents in Trauma Patients
Michael C. Huang, Mathieu Laroche, and Geoffrey T. Manley
............................................................................................................. 331
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Intraoperative Cranial-Specific Patient/Case Examples</td>
<td>343</td>
</tr>
<tr>
<td>Mark G. Hamilton, John G. Golfinos, Graham F. Pineo,</td>
<td></td>
</tr>
<tr>
<td>and William T. Couldwell</td>
<td></td>
</tr>
<tr>
<td>25 Risk of Anticoagulants and Antiplatelet Agents in Spine Surgery</td>
<td>353</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td>Aaron Hockley, Perry Dhaliwal, and W. Bradley Jacobs</td>
<td></td>
</tr>
<tr>
<td>26 Intraoperative Spine Surgery–Specific Patient/Case Examples</td>
<td>367</td>
</tr>
<tr>
<td>W. Bradley Jacobs</td>
<td></td>
</tr>
<tr>
<td>27 Risk of Anticoagulants and Antiplatelet Agents in Patients with</td>
<td>375</td>
</tr>
<tr>
<td>Brain and Spinal Catheters</td>
<td></td>
</tr>
<tr>
<td>Benjamin A. Rubin and Jeffrey H. Wisoff</td>
<td></td>
</tr>
<tr>
<td>28 Hematologic Adjuvant Treatment for Preventing and Treating Blood</td>
<td>384</td>
</tr>
<tr>
<td>Loss in Pediatric Neurosurgery</td>
<td></td>
</tr>
<tr>
<td>Julia Sharma, John R.W. Kestle, and Ash Singhal</td>
<td></td>
</tr>
<tr>
<td>29 Pediatric Neurosurgery–Specific Patient/Case Examples</td>
<td>395</td>
</tr>
<tr>
<td>Mark G. Hamilton and John R.W. Kestle</td>
<td></td>
</tr>
</tbody>
</table>

Index                                                                 | 405  |
The history of techniques and efforts used to stop bleeding and to promote coagulation is as old as the history of surgery itself. Without demonstrated success in these areas, the specialty of neurosurgery would not have progressed as quickly nor as effectively as it has. To this end, we owe a great debt of gratitude to those pioneers in our specialty—and other disciplines, who have helped us overcome the challenges of surgical bleeding when it occurs, and who have defined the thrombolytic pathways leading to optimum control of prothrombotic conditions.

As a trainee in neurosurgery, I can recall the difficulty encountered in trying to stop the profound blood loss from a metastatic spinal hemangiopericytoma in a 67-year-old woman undergoing a decompressive thoracic laminectomy—this was my introduction to the true value of packing with topical hemostatic agents. I remember the calls to the neurosurgical wards to examine postoperative patients with calf pain complaining of acute shortness of breath; these patients were precariously positioned between having good outcomes from their procedures and suffering severe morbidity depending on how swiftly the diagnosis of deep venous thrombosis and pulmonary embolus was made and the administration of anticoagulation agents was given. I have witnessed acute presentations of significant intracranial and spinal hemorrhages in patients either spontaneously or following mild or minimal trauma—only to diagnose one of the coagulation factor deficiency syndromes in the postoperative period. And, as with all neurosurgeons who have practiced these past 25 years or more, I have been the beneficiary of the innovations in hand-held electrocoagulation devices which have come to my rescue in more situations than I can bear to recount over the course of my career. I daresay that, as neurosurgeons, all of us are obsessed with the topics of hemostasis and coagulation, given the unique and unforgiving substrate that is the human central nervous system.

Now, for the first time, Hamilton and colleagues have provided us with a comprehensive, multi-authored textbook that provides neurosurgeons with the definitive resource to which to refer for all aspects of bleeding and coagulation in neurosurgery. While there may have been previous publications and reviews on topics contained within this *Handbook*, the compilation of materials herein is not only timely given the many recent advances in our understanding of the coagulation cascade in neurosurgical patients, but also highly informative given the case-based chapter format and the practical “hands-on” approach to solving bleeding and coagulation problems in our patients. In addition, each chapter is highlighted with “Key Points” that succinctly summarize the authors’ main messages and “Review Questions” that test the reader in a highly constructive and educational manner.

Perhaps the most attractive feature of this *Handbook* is the logical sequence in which information is presented. The basic science, pathophysiology, and pharmacology of the coagulation system are followed by highly practical topics that will assist all neurosurgeons in caring for their patients better. In a sense, in reading through these materials, I felt as though I were immersed in an intensive course on bleeding and hemostasis, yet at the same time being “fast-tracked” for information gathering, review, and understanding. Our world as neurosurgeons has changed, and we can succeed now where previously it was impossible, thanks to the tremendous advances that have taken place in our understanding of the management
of bleeding and coagulation in our patients. I applaud the editors of this unique textbook for their insights into the organization of the information and for presenting it in a manner which is accessible, comprehensive, and highly informative. It is doubtful that another text on this topic will be required for quite some time.

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Preface

The topic of this book is fundamental to all of neurosurgical care. We, as neurosurgeons, are challenged every day with the task of mitigating the risks of bleeding and thrombosis in our patients. It is the very nature of neurosurgery that this complicated dual-edged sword is encountered in all of our patients, of all ages, in all neurosurgical subspecialties and in all aspects of neurosurgical care. It is therefore puzzling that no dedicated resource has developed that would pull all of these difficult elements together to provide a comprehensive reference that can provide management recommendations for neurosurgeons. With this book, we undertook the task to fill this void.

The chapters are presented so that you can easily find background information or go directly to a specific patient-care relevant topic. The authors of each of the core chapters have provided a list of “key points” and some questions to help you evaluate your understanding of the material. In addition to these core chapters, there are four case-based chapters (cranial, neuroendovascular, spinal, and pediatric) that allow an opportunity to demonstrate the real practice of these patient-care recommendations.

The first section reviews and reminds us of the importance of an evidence-based approach while sorting through the medical literature that exists regarding this complex topic. This tool allows us to move beyond our potentially biased and subjective strategies and use the best quality information that is available for patient management recommendations. The expert authors of the chapters in this section were frequently challenged by the lack of good clinical trials of the type that can lead to high-grade recommendations. However, with this tool of evidence-based medicine, they are able to convey the strength of the recommendations they are providing to help guide your interpretation.

Section II provides the hematological background required to understand the clinical aspects of bleeding and coagulation. These five chapters will guide you through the coagulation system, how to assess the coagulation system in the preoperative patient, and the effects of the various drugs and herbal products that affect coagulation. All of these topics have significant impact on preoperative, intraoperative, and postoperative care.

Section III includes three chapters that review principles of blood loss and blood and volume replacement. They provide a comprehensive and practical review of this important and clinically relevant topic.

The next two sections introduce and provide a broad overview of thrombosis and bleeding in the neurosurgical patient. Section IV tackles both prevention and management of both deep venous thrombosis (DVT) and pulmonary embolism (PE) and management of cranial venous sinus thrombosis. We also examine the challenges associated with managing antiplatelet and anticoagulant medications in patients with cardiac disease. Neurosurgeons are frequently faced with evaluating not just the effects of these medications on the neurosurgical condition, but also the consequences of the underlying cardiac disease issues associated with discontinuing or reversing the effect of these drugs.

Section V in has four chapters that establish the groundwork for prevention and management of bleeding in the neurosurgical perioperative period. These authors examine strategies for reversal and resumption of anticoagulant and antiplatelet agents in neurosurgical patients and provide preoperative and intraoperative strategies for preventing blood loss. The chapters in Sections IV and V are “meaty”
and provide the necessary practical evidence to help us understand the big picture issues.

The final section focuses all the previous work and applies it to specific neurosurgical conditions. Here we examine the particular bleeding and coagulation issues relating to brain tumor patients, patients with neurovascular disorders, brain trauma, spinal surgery, brain and spinal catheters, and pediatric neurosurgery patients. This section distills the work of previous chapters to provide clarity with the application of this information to these specific aspects of neurosurgical care. Among these chapters, you will also find four case-based chapters that demonstrate real practice experience dealing with these issues.

As we have worked with the authors who contributed to this book, we have witnessed the emergence of a number of new anticoagulant agents have been included to keep the book as relevant as possible. While it is possible that newer agents will emerge over the next few years, the information presented will remain germane. Principles of management for thrombosis and bleeding in neurosurgical patients will not change. The current most common surgical strategies and pharmacologic agents are not evolutionary, but rather have been established practice for decades. However, it is important to keep vigilant for new drugs and carefully scrutinize effects on the neurosurgical condition and the balance of potential benefit with harm. It is also useful to remember that not all new things are necessarily better and all require careful evaluation. We hope this book provides you with a valuable reference to which you can turn for guidance with regard to these topics.

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<thead>
<tr>
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\(^1\)France, The Netherlands, and Spain; \(^2\)Germany and Austria; \(^3\)Denmark, Sweden, Finland, Norway, Italy, and Iceland; \(^4\)United Kingdom
I
Evidence-Based Medicine
Evidence-based medicine (EBM) has been widely promoted as an ideal in clinical practice. We are called to judiciously combine the best available evidence with clinical expertise and our patient’s values to deliver the best care possible. Without incorporating current evidence, clinical practice is at risk of becoming stale and outdated. However, without also drawing from clinical expertise, evidence cannot be safely applied, as even the best research may be inappropriate for an individual patient or clinical scenario. Thus, proper practice requires the integration of external evidence, clinical experience, and patient factors into informed decision making.

The modern EBM movement was born from legitimate concern that the ongoing and unchallenged use of unproven therapies would result in undue harm and missed opportunities to adopt more effective interventions. As such, early proponents of EBM called for evaluation of treatments through systematic and unbiased methods, and appealed to medical practitioners to continually update and appraise their own knowledge. Although the philosophical origins of EBM are not new, it has only been since the late 20th century that evidence-guided practice has been widely promoted in medicine as an ideal over authoritative teaching alone.

Over the last two decades, EBM has become the cornerstone to many undergraduate, postgraduate, and continuing medical education programs. Of note, the deliberate introduction of EBM into medical curricula and practice has been associated with improvements in knowledge acquisition, clinical care, and patient outcomes. Indeed, the evolution of EBM has had a profound impact on medicine today.

Adopting Evidence-Based Medicine and Its Challenges

The practice of EBM involves several interrelated steps, which broadly include asking an appropriate clinical question, retrieving the pertinent evidence, appraising its quality, translating evidence into practice, and evaluating the resulting outcome (Table 1.1). Admittedly, however, the adoption of EBM has faced some resistance. Some critics have voiced concerns that EBM is impractical given (1) the severe time constraints in typical busy clinical practices; (2) the often unreliable or discredited external evidence; and (3) the difficulties in applying discrete, one-dimensional studies to patients with complex, clinical conditions. This chapter systematically addresses these perceived challenges and offers practical solutions to help practitioners effectively access, appraise, and apply evidence to patient care.
Evidence-Based Medicine

Information Management

Perhaps the greatest challenge to pursuing EBM is the time constraints that most clinicians face in a busy clinical practice.\textsuperscript{15–17} Further, the volume of information that is presented to clinicians is increasing at an extraordinary pace as we are witnessing an unprecedented growth in scientific discovery.\textsuperscript{18,19} It is, therefore, of utmost importance to identify efficient and reliable sources of evidence that can quickly provide relevant answers to clinical questions.

As opposed to traditional textbooks (which are quickly outdated), optimal resources should feature the combination of current evidence-based content and easy accessibility.\textsuperscript{3} Examples of these resources include systematic reviews (e.g., \textit{Cochrane Reviews}), evidence-based synopses of the literature (e.g., American College of Physicians [ACP] Journal Club), and systems-based resources (e.g., clinical practice guidelines and updated evidence-based handbooks that explicitly cite evidence to support claims; this handbook is one such example).\textsuperscript{3} Although it is occasionally necessary to refer to original research articles for news that is “hot off the press” or for particularly specialized information, the trade-off is that of convenience. In this respect, the value of librarians and medical informaticians in assisting with information retrieval of primary data cannot be overstated. Library services facilitate information retrieval, integration of evidence into practice, and decision making, and thus have a positive impact on patient outcomes.\textsuperscript{20–22}

However, for most clinicians, routinely seeking out primary evidence to answer every clinical question, even when provided with research assistance, is impractical. Most full-time clinicians, even those who are enthusiastic about EBM, rarely have time to search and review relevant, original research.\textsuperscript{23–25} Advocates and leading enthusiasts of EBM have long acknowledged this barrier.\textsuperscript{23,26} Although it may be unrealistic to expect everyone to be “evidence-based practitioners” (i.e., those who are able to seek out and appraise raw evidence from scratch), all care providers should at least be taught to be “evidence users” (i.e., practitioners equipped with tools to flag important studies and trained to incorporate evidence into practice).\textsuperscript{23} Accordingly, information management is paramount to achieving this latter goal.\textsuperscript{23–26} Reassuringly, “evidence users” who refer to secondary sources for pre-appraised evidence can still become highly competent, up-to-date practitioners who are able to deliver evidence-based care.\textsuperscript{23}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
Step & Action \\
\hline
1 & Asking a clearly focused clinical question, considering the patient (or problem), intervention (or exposure), comparator, and outcome \\
\hline
2 & Searching for the best available evidence \\
\hline
3 & Critically appraising the evidence for its validity, importance, and applicability \\
\hline
4 & Integrating the evidence with clinical expertise and patient values into clinical practice \\
\hline
5 & Evaluating the outcome \\
\hline
\end{tabular}
\caption{The Process of Practicing Evidence-Based Medicine}
\end{table}

Along these lines, this handbook is a clear example of one of the many new and evolving information systems designed to facilitate evidence-based practice amidst the time constraints we all face. This book was written to serve as a credible resource of evidence-based content where the best and most relevant studies have been pre-appraised, graded, and summarized by clinical experts to provide quick and reliable answers to important questions related to bleeding and coagulation in the neurosurgical setting.

**Critical Appraisal**

Another challenge raised by critics of EBM is that research discoveries may be unreliable and sometimes even misleading. Indeed, there are numerous examples of studies that later became discredited and of reputedly evidence-based guidelines that, over time and unexpectedly, needed to be changed. For example, based on a prospective cohort study conducted decades ago, there was a long-held belief that abrupt smoking cessation within 8 weeks of surgery was harmful and increased the risk of postoperative pulmonary complications,\(^27\) presumably because of decreased coughing and increased sputum production.\(^28\) Physicians were cautioned against advising patients to stop smoking shortly before surgery.\(^27,28\) However, subsequent studies have yielded contrary results. Two randomized controlled trials (RCTs) have shown that smoking cessation within 8 weeks of surgery did not increase the rate of pulmonary complications but rather reduced overall perioperative morbidity.\(^29,30\) Likewise, recent systematic reviews and meta-analyses have similarly concluded that short-term preoperative smoking cessation is likely beneficial, with no indication of harm.\(^31–33\) This example illustrates how some clinicians have become understandably frustrated when “best evidence” changes, leaving them to wonder what to believe or trust.

Indeed, these research discrepancies may be related to problems inherent to study design or analysis (e.g., confounding and bias in observational studies) or attributed to the inappropriate interpretation of results (e.g., inferring causation from data that merely show association). Fortunately, these discrepancies are rarely the result of deliberate scientific misconduct or fraud. Nonetheless, we should not allow these problems to dissuade us from keeping up-to-date. Rather, these problems simply highlight the importance of critical appraisal to evaluate study importance and validity—that is, to understand the parameters and limitations of each study and to interpret the implications of the results. Furthermore, critical appraisal involves grading studies according to the strength of the underlying study design, identifying possible sources of bias, and determining if the resulting conclusions are appropriate.\(^34\)

Many clinicians have difficulty grasping the complexities of the different study designs reported in the literature. As an overview, primary evidence can broadly come from experimental studies (e.g., RCTs), observational studies (e.g., cohort, case-control studies, quasi-experimental designs), and nonsystematic observations (e.g., case reports and case series). All observational studies are inherently subject to confounding and possible bias because of baseline differences in the characteristics between comparison groups, which may, in turn, threaten a study’s validity and potentially result in incorrect inferences.\(^35\) Addressing this issue, statisticians have developed increasingly sophisticated analytical techniques to account for imbalances between groups using matching, multivariable regression analysis, propensity scores, and instrumental variables. Nonetheless, it is impossible to absolutely
Evidence-Based Medicine

guarantee that an observational study is free from all potential confounding and bias regardless of the extent of statistical adjustment. It is for this reason that RCTs are commonly heralded as the gold standard of study designs, as they are the least susceptible to confounding and bias when properly designed and with adequate randomization. However, a common weakness of the RCT is that patient selection criteria is often intentionally narrow (so as to minimize variability and maximize statistical efficiency), thus limiting the generalizability of the results. Still, it is widely accepted that a properly conducted RCT is more valid than observational studies or nonsystematic clinical observations.

With this in mind, many clinicians commonly refer to a hierarchical pyramid of evidence to determine the strength of a study. First introduced in 1979,35 this concept has been refined over the years, and is presently used in a wide variety of guidelines.36,37 These systems commonly place RCTs in a pyramidal hierarchy above observational studies (Table 1.2). It should be noted, however, that although it is true that RCTs are a critical component of the evidence base for questions of therapeutic efficacy, it may be inappropriate for other questions (e.g., of prognosis or natural history where exposures cannot be controlled, or where RCTs cannot be ethically conducted).38 In situations where RCTs are neither feasible nor practical, observational designs may be superior. In this regard, dedicated research registries with rich clinical data have greatly facilitated quality improvement, post-trial evaluations in “real-world” settings, evaluations of process of care, and surveillance for rare outcomes. Thus, it is increasingly apparent that registries and databases are indispensable tools that offer unique advantages over even well-designed trials in some circumstances.

Furthermore, although RCTs may potentially provide the highest quality of evidence, not all RCTs are properly conducted or analyzed. Grading the quality of evidence, therefore, should not be based entirely on the study design alone.34,39–41 In this regard, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group has identified the shortcomings of using a rigid evidence pyramid and take into account other important study factors in addition to design.42,43 For RCTs, study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias are taken into consideration; for observational studies, the magnitude of effect, the presence of a dose–response relationship, and the impact of potential biases are taken into consideration. Accordingly,

Table 1.2 Possible Hierarchy of Evidence for Therapeutic Studies

<table>
<thead>
<tr>
<th>Strength</th>
<th>Design</th>
</tr>
</thead>
</table>
| Strongest | N of 1 randomized trial  
Systematic reviews of randomized trials  
Single randomized trial  
Systematic review of observational studies addressing patient-important outcomes  
Single observational study addressing patient-important outcomes  
Physiological studies |
| Weakest | Unsystematic clinical observations |

the grading of a study may shift down or up given the presence or absence of these factors. Of note, the current American College of Chest Physicians (ACCP) antithrombotic therapy and prevention of thrombosis guidelines have presented clinical recommendations based on the described GRADE methodology (Table 1.3). These ACCP guidelines, a mature clinical practice initiative, are particularly relevant to the content of this handbook.

Thus, this book follows a similar template, where appropriate; statements relating to prognosis, diagnosis, harm, and therapy are accompanied by a clear articulation and grading of the evidence. Understanding how to correctly assess the quality and strength of evidence is foundational for the practice of EBM.

### Table 1.3 Evidence Grading System for American College of Chest Physicians (ACCP) Guidelines

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Benefit Versus Risk and Burdens</th>
<th>Strength of Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, high-quality evidence (1A)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence (1B)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or very strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Strong recommendation, low- or very-low-quality evidence (1C)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence</td>
<td>Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
</tr>
</tbody>
</table>

(Continued on page 7)
The final step in practicing EBM is assessing evidence for its applicability to specific clinical situations. Although the concept of validity addresses whether a study is able to answer the desired question internally, generalizability assesses how well the results apply externally. Misapplication of evidence, by ignoring clinician

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Benefit Versus Risk and Burdens</th>
<th>Strength of Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak recommendation, high-quality evidence (2A)</td>
<td>Benefits closely balanced with risks and burden</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
<td>The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Weak recommendation, moderate-quality evidence (2B)</td>
<td>Benefits closely balanced with risks and burden</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or very strong evidence from observational studies</td>
<td>Best action may differ depending on circumstances or patient or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Weak recommendation, low- or very-low-quality evidence (2C)</td>
<td>Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence</td>
<td>Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.</td>
</tr>
</tbody>
</table>

**Abbreviation:** RCT, randomized controlled trial.


## Table 1.3 (Continued) Evidence Grading System for American College of Chest Physicians (ACCP) Guidelines

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### Translating Evidence-Based Medicine to Patient Care

The final step in practicing EBM is assessing evidence for its applicability to specific clinical situations. Although the concept of validity addresses whether a study is able to answer the desired question internally, generalizability assesses how well the results apply externally. Misapplication of evidence, by ignoring clinician
experience, patient values, or clinical circumstance, has resulted, unfortunately, in the common misperception that EBM is no more than “cookbook” medicine. Translating evidence into clinical care is further complicated by the fact that it can be challenging to apply findings from discrete studies directly to patients with complex and competing conditions. Although safely and properly applying evidence to patient care can be a nuanced process, there are four guiding principles that are useful to consider:

First, to determine whether the findings of a particular study are applicable to an individual patient, rather than poring over all the granular inclusion and exclusion criteria of a study, a good approach is to simply ask, “Is my patient’s underlying condition so different that this study cannot provide any guidance?” As a general rule, if the disease pathogenesis, patient physiology, and environmental conditions are similar, the study results are likely to be externally generalizable. However, clinicians still have the conservative tendency to limit their use of evidence-proven treatments to only “ideal” patients who would have met all the strict study enrollment criteria. Although some variation between the treatment response of a specific patient and the treatment response of subjects reported in a study is to be expected, these differences tend to be quantitative (i.e., in the degree of risk and responsiveness) rather than qualitative (i.e., opposite or no response) in nature. Therefore, in general, therapies that are found to be beneficial in a narrow range of patients typically have a broader applicability in actual practice.

Second, local facilities and organizational factors must be considered. Accordingly, it is necessary to determine if a treatment is feasible within a specific care setting. For instance, it is moot point to consider prescribing to the patient a medication that is not available or prohibitively expensive, no matter how convincingly beneficial it may appear to be. Similarly, although a new surgical intervention that is reported to unequivocally reduce mortality may be appealing, if there is no local experience or available equipment to perform the procedure, then blindly applying the technique may prove to be more detrimental than beneficial, as perioperative complications may outweigh possible benefits. In such cases, an alternative and more feasible option may be to refer eligible patients to another center with the relevant expertise.

Third, the risk–benefit ratio should be estimated for an individual patient. This can sometimes be challenging, however, because of selective reporting of outcomes in studies and the wide variety of metrics used. Nonetheless, whenever possible, the baseline risk for a patient and expected therapeutic effects should be determined. Although both relative and absolute effect estimates are legitimate ways of reporting data, absolute estimates (e.g., number needed to treat [NNT], number needed to harm [NNH], absolute risk difference, etc.) are typically preferable, as they provide useful estimates of the benefit (or harm) that is expected from a particular treatment (or exposure) while also reflecting average baseline risk over a specific timeframe. Moreover, an inherent advantage to using NNT (or NNH) is that it provides frontline clinicians with an intuitive summary of the difference in efficacy between a treatment and comparator, and is often easier to understand for patients. As a caveat, however, it should be noted that NNT and NNH vary according to baseline risk. Therefore, if a particular patient’s characteristics are substantially different from those of the subjects in a specific study, it may be difficult to reliably estimate actual risks and benefits. In such cases, clinical judgment should be exercised.
Fourth, but equally important, it is crucial to incorporate a patient's unique values into decision making. Admittedly, the optimal method to incorporate patient preferences into the decision-making process remains uncertain and continues to be studied.\textsuperscript{3,48} Nonetheless, it should be noted that patient involvement in the decision-making process has been consistently shown to improve quality of life and health outcomes,\textsuperscript{53–57} thus highlighting the importance of this aspect of care.

**Conclusion**

We are called to judiciously combine the best available evidence with clinical expertise and our patient's values to deliver the best care possible.\textsuperscript{2,3} High-quality care is based on practice that is consistent with best evidence. As clinicians, we should develop a habit of constantly revisiting our basic assumptions and re-appraising the state of our knowledge with the goal of delivering optimal care as informed by the best available evidence. With the flow of new information, we gain greater insights into medicine, refine our practices, and continue to explore new paradigms of care. As such, the aim of this handbook is to provide current, evidence-based content to guide the best management of bleeding and thrombosis in neurosurgical care.

**KEY POINTS**

- Evidence-based medicine seeks to integrate relevant external evidence, clinical experience, patient values, and clinical context together.
- Evidence-based, pre-appraised summaries of the literature are valuable. They provide quick and reliable answers to important clinical questions.
- Critical appraisal of the literature is necessary to determine the validity and importance of studies.
- It is important to consider the applicability of evidence, the feasibility of an intervention, the risk–benefit ratio, and individual patient values and preferences to effectively translate evidence into patient care.

**REVIEW QUESTIONS**

1. Which of the following resources is *least likely* to provide current and relevant evidence-based content?
   A. A traditional textbook
   B. A systematic review published by *The Cochrane Collaboration*
   C. A secondary synopsis by the ACP Journal Club
   D. An updated evidence-based handbook

2. Which of the following study designs is *least susceptible to confounding* (i.e., important baseline differences between comparison groups)?
   A. Prospective cohort study
   B. Historical cohort study
   C. Randomized controlled trial
   D. Case-control study
3. Which of the following study designs is most susceptible to confounding (i.e., important baseline differences between comparison groups)?
   A. Prospective cohort study
   B. Historical cohort study
   C. Randomized controlled trial
   D. Case-control study

4. Which of the following is not a method to account for differences between treatment groups within a study?
   A. Intention-to-treat
   B. Matching
   C. Regression modeling
   D. Propensity scores

5. If properly conducted and analyzed, which of the following generally provides the strongest evidence for therapeutic efficacy?
   A. Cohort study
   B. Randomized controlled trial
   C. Systematic review and meta-analysis of cohort studies
   D. Systematic review and meta-analysis of randomized controlled trials

6. Which of the following provides an estimate of absolute risk?
   A. Odds ratio
   B. Hazard ratio
   C. Risk difference
   D. Risk ratio

7. Which of the following is generally the least important consideration when applying evidence at a patient's bedside?
   A. Meeting the exact same strict inclusion criteria as the study protocol of interest
   B. Identifying complex and competing conditions using clinical experience
   C. Integrating patient preferences and values
   D. Determining feasibility based on local and organization factors

Acknowledgments

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ANSWER KEY

1. A
2. C
3. D
4. A
5. D
6. C
7. A
II

Hemostasis and Coagulation
Hemostasis mechanisms prevent excessive blood loss after vascular injury while also preventing an inappropriate thrombotic response. This equilibrium is maintained by balanced interactions among vascular endothelium, platelets, and coagulation proteins that are present in blood plasma. Vascular trauma initiates primary hemostasis, which involves adhesion of platelets to damaged endothelium followed by platelet aggregation. The platelet thrombus is subsequently reinforced by a fibrin meshwork generated by the coagulation mechanism (secondary hemostasis). Vascular patency is restored by the fibrinolytic mechanism. Defects in either primary hemostasis (platelet number or function) or secondary hemostasis (coagulation factor deficiency) may lead to excessive bleeding.1

Primary Hemostasis

Vascular injury results in exposure of subendothelial components (e.g., collagen) that induce binding of von Willebrand factor (vWF) to platelets. The platelet vWF receptor, glycoprotein (GP)1b is required for this interaction. The subendothelium–vWF–GP1b mechanism leads to platelet adhesion. Subsequent platelet activation results in platelet aggregation, an event mediated by fibrinogen and platelet GPIIb/IIIa. Deficiency of GP1b, GPIIb/IIIa, vWF, or thrombocytopenia, or platelet dysfunction may result in defective primary hemostasis and bleeding.1

Secondary Hemostasis

Reinforcement of the platelet thrombus requires initiation of the coagulation mechanism by tissue factor, a protein not normally exposed to blood. However, with vascular injury, tissue factor activity is expressed and initiates the process of thrombin generation. Blood coagulation involves a cascade of enzymatic conversions of an enzyme precursor (zymogen) to a protease (active enzyme), which subsequently activates another zymogen. This cascade ultimately leads to conversion of prothrombin to thrombin and, finally, to conversion of soluble plasma fibrinogen to an insoluble fibrin clot.2

Platelet Physiology and Function

Blood platelets are anucleate disk-shaped cells generated by bone marrow megakaryocytes. With megakaryocyte maturation, the megakaryocyte cytoplasm demar-
cates into individual platelets that are shed into the circulation. The platelet membrane contains key GP receptors that mediate primary hemostasis, GP1b and GPIIb/IIIa. Platelets also contain granules that participate in primary hemostasis: α-granules containing proteins such as vWF and platelet factor 4, and δ-granules containing adenosine diphosphate (ADP), adenosine triphosphate (ATP), and serotonin. Release of serotonin from platelets mediates vasoconstriction following vascular injury.\(^1\)

Following platelet adhesion to the damaged vessel wall, platelet activation occurs. Platelet activation is associated with granule secretion (platelet release reaction) and stimulation of prostaglandin synthesis. In the latter mechanism, arachidonic acid generated from platelet phospholipids is converted by platelet cyclooxygenase and thromboxane synthase to thromboxane A\(_2\), a potent platelet activator and vasoconstrictor. The granule release reaction and thromboxane A\(_2\) synthesis are also coordinated with expression of the GPIIb/IIIa receptor, fibrinogen binding to platelets, and platelet aggregation. These events result in a rapidly propagating platelet thrombus and cessation of bleeding.\(^2\) The activated platelet surface expresses receptors for coagulation proteases that ultimately generate fibrin to consolidate the platelet thrombus. Fig. 2.1 summarizes the hemostasis events following vascular injury. Although shown as discrete events, primary and secondary hemostasis occur nearly synchronously.

**Fig. 2.1a–d** Summary of the hemostatic response to vascular injury. (a) In the normal state, vascular endothelium is intact, blood flow is normal, and platelets circulate in a nonactivated state. (EC, endothelial cells.) (b) With vascular injury, subendothelial components such as collagen are exposed, leading to platelet adhesion (mediated by von Willebrand factor [vWF] and platelet glycoprotein [GP]Ib). (c) With platelet activation, granule contents are released (adenosine diphosphate [ADP], serotonin), leading to vasoconstriction and platelet aggregation (mediated by fibrinogen and platelet GPIIb/IIIa). Generation of thromboxane A\(_2\) recruits additional platelets into the growing platelet thrombus. (d) Activation of platelets promotes initiation of coagulation in which thrombin generation leads to fibrin formation, reinforcement of the platelet thrombus, and subsequent clot retraction and consolidation.
Coagulation Pathways

Activation of coagulation occurs by two pathways. The major pathway involves tissue factor expression that in the presence of factor VII (or activated factor VIIa) rapidly activates factor X to factor Xa, and factor IX to factor IXa. In the presence of factor V (Va), factor Xa converts prothrombin to thrombin. Thrombin cleaves fibrinogen to generate soluble fibrin, activates platelets, and also activates factors V, VIII, XI, and XIII. Soluble fibrinogen is cross-linked by factor XIIIa to generate the insoluble fibrin clot. These events are summarized in Fig. 2.2.

Alternately, thrombin can be generated by the factor XII pathway (Fig. 2.2). An abnormal surface converts factor XII to XIIa. Factor XII converts prekallikrein to kallikrein, which amplifies factor XII activation, leading to activation of factor XI. These reactions require a cofactor protein—high molecular weight kininogen (HMWK). Factor XIa subsequently activates factor IX, and factor IXa in the presence of factor VIII (VIIIa) converts factor X to Xa.

Although important for in vitro thrombin generation, the factor XII pathway is not important for in vivo thrombin formation because deficiencies of factor XII, prekallikrein, and HMWK are not associated with a bleeding disorder. This implies that there are in vivo pathways to initiate activation of factor XI, because factor XI deficiency does result in a bleeding disorder. Current data suggest that thrombin generated by the tissue factor pathway activates factor XI in a feedback loop in addition to factors V and VIII to amplify coagulation (Fig. 2.2).

![Coagulation mechanism](image-url)

**Fig. 2.2** The coagulation mechanism. Coagulation is initiated in vivo by expression of tissue factor (TF) activity. The TF–factor VII complex activates factors IX and X to IXa and Xa before inhibition of TF activity by tissue factor pathway inhibitor occurs. Thrombin generated by initial TF feeds back to activate factors V, VIII, and XI to amplify coagulation. Factor XII initiated-coagulation (with prekallikrein [PK] and high molecular weight kininogen [HMWK]) is important when artificial surfaces are present, but not for in vivo coagulation. Soluble fibrin generated by thrombin cleavage of fibrinogen is cross-linked by factor XIIIa to produce the insoluble fibrin clot. (Fibrin, soluble fibrin; Fibrin, insoluble fibrin.)
Fibrinolysis

After the hemostatic plug is formed and bleeding controlled, vascular repair begins with lysis of the fibrin clot. Thrombin formation stimulates endothelial cell secretion of tissue plasminogen activator (tPA). Plasminogen and tPA diffuse within and bind to the fibrin clot, where tPA stimulates activation of plasmin from plasminogen, resulting in physiological fibrinolysis. Fibrinolytic inhibitors to tPA and plasmin (plasminogen activator inhibitor and $\alpha_2$-antiplasmin, respectively) restrict fibrinolysis to the clot (Fig. 2.3).

Coagulation Regulatory Mechanisms

The coagulation cascade and platelet function are modulated by regulatory mechanisms that maintain blood fluidity (Fig. 2.4). Most of these mechanisms involve vascular endothelium and include the protein C pathway, antithrombin pathway, tissue factor pathway inhibitor, and fibrinolysis (discussed above). Endothelium also regulates platelet activation by at least three mechanisms: secretion of an antiplatelet prostaglandin—prostacyclin, secretion of nitric oxide, and expression of CD39, an adenosine diphosphatase (ADPase) with antiplatelet properties. Many of these mechanisms are clinically important because deficiency of certain regulatory proteins (also called “natural anticoagulants”—protein C, protein S, antithrombin) is associated with a hypercoagulable state and an increased risk of thrombosis.

The protein C pathway involves three coagulation proteins: protein C, protein S, and thrombomodulin. When thrombin generation occurs, thrombin binds to thrombomodulin; this complex converts protein C to activated protein C, a potent anticoagulant. In the presence of protein S, activated protein C inactivates factors Va and VIIIa, resulting in inhibition of thrombin formation. This feedback inhibition mechanism is considered important in regulating thrombin function and preventing excessive fibrin deposition.

The antithrombin pathway is another natural anticoagulant mechanism. The luminal surface of vascular endothelium expresses heparan sulfate molecules that catalyze antithrombin inhibition of thrombin and other activated clotting factors.

Following initial expression of tissue factor activity, this procoagulant is suppressed by tissue factor pathway inhibitor (Fig. 2.2).
Platelets

Platelet counts are usually obtained from complete blood count (CBC) tests in which automated particle counters quantitate platelets based on cell size. In vivo tests of platelet function such as the bleeding time are currently viewed as unreliable because they do not accurately predict excessive bleeding or discriminate patients with platelet dysfunction from people with normal platelet function. In vitro tests of platelet function such as the Platelet Function Analyzer (PFA)-100® (Siemens Medical Solutions USA, Inc., Malvern, PA) may be more useful than the bleeding time test, but a consensus panel evaluating platelet function testing does not recommend the PFA-100 test for routine clinical use.

The gold standard for measuring platelet function is light-transmission platelet aggregation. Either citrate-anticoagulated whole blood or platelet rich plasma is treated with various platelet agonists (stimuli), such as ADP or collagen, and the extent of platelet aggregation is quantitated. Newer methods to assess platelet function are available (e.g., VerifyNow™, Accumetrics, San Diego, CA), but studies demonstrating sufficient validation or other utility of these methods in altering clinical outcomes are lacking.
Coagulation Factors

The two screening tests for measuring coagulation factor levels are the prothrombin time (PT) and partial thromboplastin time (PTT) assays. The PT assay measures the factor VII pathway and common pathway (factors X, V, prothrombin, and fibrinogen) (Fig. 2.4). Prolonged PT values usually indicate decreased levels of at least one of the above factors.7

The PTT assay measures the factor XII pathway (with prekallikrein and HMWK); factors XI, IX, and VIII; and the common pathway (factors X, V, prothrombin, and fibrinogen) (Fig. 2.5). Prolonged PTT values usually indicated decreased levels of at least one of the above factors.7

Interpretation of the PT and PTT Assays in Patients with Bleeding Disorders

When combined with the platelet count, PT and PTT assays can be useful in evaluating patients with possible hemostatic disorders. Structural bleeding from lacerated blood vessels and arteriovenous malformations should always be considered before assuming that a patient has a hemostatic defect. In this regard, preoperative assessment of the patient’s hemostatic history is valuable (see Chapter 3).

If abnormal hemostasis is thought to be likely, Table 2.1 presents a strategy that may be useful in suggesting possible hemostatic disorders and their laboratory

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**Fig. 2.5** Assay of the coagulation mechanism by the PT and PTT tests. The PT assay measures the factor VIIa pathway and common pathway (*small loop*). The PTT assay measures the factor XII pathway, including prekallikrein; high molecular weight kininogen; factors XI, IX, and VIII; and the common pathway (*large loop*). Tissue factor and factor XIII activities are not measured by either the PT or PTT assay.
Table 2.1 Interpretation of Hemostasis Screening Test Results in Patients with Bleeding Disorders and Suggested Subsequent Testing

<table>
<thead>
<tr>
<th>PT</th>
<th>PTT</th>
<th>Platelet Count</th>
<th>Frequency</th>
<th>Differential Diagnosis</th>
<th>Subsequent Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>Common</td>
<td>Factor VII deficiency (liver disease, vitamin K deficiency, warfarin)</td>
<td>Liver panel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
<td>Factor VII inhibitor, inherited factor VII deficiency, DIC, super warfarin</td>
<td>Factor VII, D-dimer, brodifacoum level</td>
</tr>
<tr>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>Common</td>
<td>Deficiency of factors VIII, IX, XI, vWD, heparin</td>
<td>Thrombin time, factors VIII, IX, XI</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>Common</td>
<td>Vitamin K deficiency, liver disease, warfarin, heparin, superwarfarin</td>
<td>Liver panel, thrombin time, brodifacoum level</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
<td>DIC, deficiency of factors X, V, prothrombin, fibrinogen, primary fibrinolysis</td>
<td>D-dimer, factors X, V, prothrombin, fibrinogen, FDP</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>Common</td>
<td>DIC, liver disease, heparin</td>
<td>D-dimer, liver panel, thrombin time</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Common</td>
<td>vWD, acquired platelet dysfunction (drugs, uremia)</td>
<td>vWD panel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare</td>
<td>Inherited platelet dysfunction, factor XIII deficiency, vascular disorders, mild factor deficiency</td>
<td>Platelet aggregation, factor XIII, consider all factor assays</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>Common</td>
<td>Increased platelet destruction, decreased platelet production, splenomegaly</td>
<td>Consider bone marrow</td>
</tr>
<tr>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>Common</td>
<td>Myeloproliferative disorders</td>
<td>Bone marrow</td>
</tr>
</tbody>
</table>

Abbreviations: DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; vWD, von Willebrand disease.

Note: Differential diagnosis and suggested tests above assume that structural bleeding has been excluded. Warfarin and superwarfarin ingestion can be confirmed by assaying the four vitamin K–dependent factor levels: VII, X, IX, and prothrombin. Additionally, specific drug assays are available to evaluate warfarin and superwarfarin ingestion. Brodifacoum is the superwarfarin chemical responsible for the coagulopathy associated with rodenticide ingestion. Heparin presence in coagulation samples can be tested by using the thrombin time test. Platelet aggregation assays are only recommended to evaluate patients with possible inherited (not acquired) platelet dysfunction. Because the PT and PTT assays are screening tests, mild factor deficiency may not be detected by these assays, but abnormal hemostasis may still result in excessive surgical bleeding. Patients who are being evaluated for hemostatic disorders who have normal screening tests may require assay of all coagulation factor levels to achieve a diagnosis.
evaluation. For example, a patient with an isolated, prolonged PT (normal platelet count and PTT) should be evaluated for liver disease, warfarin use, vitamin K deficiency, and disseminated intravascular coagulation (DIC). For a patient with bleeding and a prolonged PTT (normal platelet count and PT), heparin should first be excluded. Next, factors VIII, IX, and XI should be assayed. A large number of patients who have normal PT, PTT, and platelet count have a potential bleeding disorder; these patients may require extensive testing before a diagnosis is made.

**KEY POINTS**

- Hemostasis is maintained by balanced interactions among vascular endothelium, platelets, coagulation proteins, and the fibrinolytic mechanism.
- Defects in either primary hemostasis (platelets) or secondary hemostasis (coagulation) may lead to excessive bleeding.
- Natural anticoagulant mechanisms (proteins C and S, antithrombin) regulate thrombin formation and, if deficient, result in a prothrombotic state.
- The most reliable test of platelet function is light transmission platelet aggregation.
- The PT and PTT assays are screening tests for the coagulation mechanism and can be used to generate a differential diagnosis in a bleeding patient.

**REVIEW QUESTIONS**

1. Primary hemostasis consists of which of the following:
   - A. Adhesion of platelets to damaged endothelium
   - B. Platelet aggregation
   - C. Development of a fibrin mesh
   - D. Von Willebrand factor
   - E. Fibrinolysis

2. Platelet aggregation is associated with:
   - A. Granule secretion (platelet release reaction)
   - B. Depression of prostaglandin synthesis
   - C. Vasodilation
   - D. Expression of GPIIb/IIIa receptor
   - E. Fibrinogen binding to platelets

3. The major coagulation pathway involves:
   - A. Factor XII
   - B. Factor VII
   - C. Factor XI
   - D. Factor V
   - E. Thrombin

4. Fibrinolysis involves:
   - A. Stabilization of the fibrin clot
   - B. Secretion of tissue plasminogen activator
   - C. Plasminogen activation to plasmin
   - D. Elevated plasminogen activator activity
   - E. Suppressed α₂-antitrypsin activity
5. The gold standard test for assessing platelet function is:
   A. VerifyNow™
   B. Platelet function analyzer
   C. Light-transmission platelet aggregation
   D. Bleeding time
   E. Partial thromboplastin time (PTT)

6. Screening tests to measure coagulation factor levels include:
   A. Bleeding time
   B. Prothrombin time (PT)
   C. Vitamin K level
   D. Partial thromboplastin time (PTT)
   E. Platelet count

References

ANSWER KEY
1. A, B, and D
2. A, D, and E
3. B, D, and E
4. B, C, and D
5. C
6. B and D
Preoperative Coagulation Assessment for the Neurosurgical Patient
Venkatesh K. Rudrapatna and George M. Rodgers

Evidence-Based Background

When a blood vessel is injured, the vascular, platelet, coagulation, and fibrinolytic systems interact in a finely orchestrated and coordinated fashion to prevent blood loss by localizing the thrombus to the site of injury. Bleeding can arise from abnormalities in any one, or a combination, of these four components of the hemostatic system. The physiology of this system is complex, and the current laboratory tests, which are widely used, cannot precisely reproduce these in vivo hemostatic processes.1

To evaluate bleeding tendencies, routine coagulation testing is often performed before surgical procedures. In most cases, this practice could reasonably be eliminated because it has been demonstrated that the best preoperative screen for bleeding disorders is a careful clinical history.2–5 Routine preoperative coagulation testing contributes little to patient care.6–9 Recently, the British Committee for Standards in Haematology1 published guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. Based on a literature review, the committee found a poor predictive value of preoperative hemostatic tests, and thus its recommendation is that patients with a negative bleeding history do not require routine coagulation screening prior to surgery. However, this recommendation was based on a small number of studies. Also recently, the Italian Society for Haemostasis and Thrombosis (SISET: Società Italiana per lo Studio dell’ Emostasi e della Trombosi)10 published guidelines for the preoperative and preprocedural assessment of the bleeding risk, with the aim of reducing the incidence of preventable bleeding complications and limiting laboratory tests to those necessary. The areas with evidence (although of low quality) included neurosurgery in adults, and demonstrated the clinical value of a good history, prothrombin time (PT), partial thromboplastin time (PTT), and platelet counts. Studies were also evaluated in children undergoing major surgery, including adenotonsillectomy and neurosurgery, and invasive procedures. There were limitations to these guidelines because all retrieved studies were of low methodological quality with a high potential for bias, because they were not conducted using blinded outcome assessments. In addition, variable criteria for the severity of bleeding events and different normal reference values of the laboratory tests were adopted.

A retrospective study of 1,211 patients undergoing neurosurgery procedures over a 1-year period was conducted at the Royal Melbourne Hospital, Victoria, Australia. Many patients’ history had clinical features indicating a potential bleeding tendency, but only a prolonged PTT, cranial surgery, and the use of antihypertensive and anesthetic drugs preoperatively predicted postoperative bleeding. Prolonged PTT was predictable based on the history in most patients.11
Thus, there are limited randomized studies assessing the utility of routine coagulation testing in the preoperative surgical patient. Data are even more limited for the neurosurgery setting.

Common and Uncommon Coagulation Tests

Common Tests

*Platelet Count*

Preoperative platelet measurement is of questionable utility, as are all other routine laboratory screening tests. However, there is a relative consensus to perform this measurement before certain surgeries on highly vascular organs such as cardiac operations and neurosurgical procedures. A normal platelet count eliminates the need for concern about the common disorder of primary hemostasis—thrombocytopenia. This baseline value can also be useful in retrospect in evaluating perioperative or postoperative bleeding, or in the case of heparin-induced thrombocytopenia where a baseline platelet count is important for diagnosis.

*Prothrombin Time*

The PT is measured using an automated analyzer. It is used to assess the extrinsic and common pathways of clotting, which consist of tissue factor and factor VII, and coagulation factors in the common pathway (factors II [prothrombin], V, X, and fibrinogen). The international normalized ratio (INR) format should only be used as a standardized measure of PT evaluation for patients on warfarin or other vitamin K antagonists.

*Activated Partial Thromboplastin Time*

The PTT is measured using an automated analyzer. It tests the integrity of the intrinsic and common pathways of coagulation. It detects deficiencies and inhibitors of the intrinsic (factors VIII, IX, and XI) and common pathway factors (including lupus anticoagulant and therapeutic anticoagulants). It also detects deficiency of factor XII, prekallikrein, and high molecular weight kininogen. Thus, the PTT detects hemophilias (deficiencies in factor VIII and IX) directly and von Willebrand’s disease indirectly. It tends to detect the more important and frequent disorders of coagulation. Hence, if only one test were to be performed to detect a disorder of coagulation, it should be the PTT rather than the PT.

*Thrombin Time*

The thrombin time (TT) measures the final step of the clotting pathway—the conversion of fibrinogen to fibrin through the addition of exogenous thrombin to the patient’s plasma. It can potentially detect significant hypofibrinogenemia, dysfibrinogenemia, excessive fibrinolysis, and fibrin degradation products. One of the major causes of a prolonged thrombin time is heparin. The presence of heparin in plasma can be confirmed using the reptilase time assay. An enzyme derived from snake venom called reptilase is used instead of thrombin in the assay. Reptilase has an action similar to that of thrombin, but unlike thrombin it is not inhibited by
heparin. A patient receiving heparin, therefore, would have a prolonged TT, but a normal reptilase time.

**Uncommon Tests**

These tests should not be performed routinely and should be ordered in consultation with a hematologist. Most of these tests have not been validated for use in the preoperative setting.

**Peripheral Blood Smear**

Review of the blood smear by a hematologist or a hematopathologist would be helpful to evaluate the etiologies of thrombocytopenia or thrombocytosis.

**Disseminated Intravascular Coagulation Panel: D-Dimer, Fibrinogen, Fibrin Degradation Products**

D-dimer is a fibrin degradation product (FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross-linked D domains of the fibrinogen protein. In disseminated intravascular coagulation (DIC), there is evidence of fibrin breakdown such as elevated level of D-dimer and FDPs. Given the massive fibrin deposition that can occur in DIC, fibrinogen levels are usually decreased. However, this is not always the case because fibrinogen is an acute-phase reactant that is increased in inflammation, and although fibrinogen values may decrease as the DIC progresses, hypofibrinogenemia is not reliably found in all cases of DIC. The gold standard for diagnosing DIC is the D-dimer assay.

**Factor Activity Levels**

Specific factor levels can be measured, including factor VIII, IX, and XI levels.

**1:1 Mixing Study**

This test is used to distinguish factor deficiency from factor inhibitor, such as the lupus anticoagulant, or specific factor inhibitors, such as antibodies directed against factor VIII. Mixing studies take advantage of the fact that factor levels that are 50% of normal yield a normal PT or PTT result. The test is done by mixing patient’s plasma 1:1 with normal plasma that contains 100% of all factor levels. Correction of the PT or PTT assay with mixing indicates factor deficiency; failure to correct indicates an inhibitor.

**von Willebrand Panel**

This panel includes an assay for von Willebrand factor (vWF) antigen (vWF:Ag), which measures the amount of vW protein, and vWF ristocetin cofactor activity (vWF:RCo) which measures the function of the vW protein. Factor VIII is also a component of the vW panel.
**Bleeding Time**

This test has been historically used to predict surgical bleeding. Although it may provide an estimate of platelet function, it is not a good screening test to predict bleeding risk. In one review of 13 studies (two of which were prospective studies) involving the bleeding time (BT) as a screening test, there was no correlation between the BT and surgical bleeding. Given that it is insensitive, invasive, time consuming, and subject to variation due to technical factors, it presently has a very minimal role in hemostasis testing, and consensus recommendations do not support using the BT test.

**Platelet Function Analyzer (PFA-100)**

This test has been reported to be superior to the BT as a screening test of primary hemostasis, and it has replaced the bleeding time for purposes of screening for von Willebrand disease (vWD) and intrinsic platelet hypofunction. However, a consensus panel of the International Society of Thrombosis and Hemostasis does not recommend use of the PFA-100 test due to the lack of studies validating its utility.

**Platelet Aggregation Studies**

This test has many technical requirements, including that the specimen must be received within 1 hour of phlebotomy, and that the patient must be fasting and not taking certain medications. The test is useful to evaluate patients with suspected inherited qualitative platelet disorders. This test may not be accurate if platelets are substantially decreased (<100,000/μL). Platelet aggregation is the gold standard for platelet function.

**Thromboelastography**

Thromboelastography has been used as a technique for over half a century to assess global blood coagulation and fibrinolysis. The development of point-of-care analyzers has rekindled interest in this test for assessment of bleeding risk. The method measures the rate of fibrin polymerization and clot strength in plasma or whole blood as reflected in viscoelastic changes within the test sample. Some studies have validated the utility of this test in the setting of hepatic surgery, especially liver transplantation. A few studies have assessed the utility of perioperative assessment of coagulation in pediatric and adult neurosurgical patients using thromboelastography. In these studies, thrombelastograph coagulation analysis gave a hint to the development of a hypercoagulable state after surgery. However, based on the limited results of these small studies, routine use of thromboelastography in the clinical setting is not currently recommended.

**Limitations of Coagulation Testing**

Coagulation screening tests can be meaningfully interpreted only with knowledge of their limitations and the relevant clinical situation. Most of these tests are in vitro laboratory assays that measure the time to clot formation in a test tube and that require the addition of exogenous reagents. Interpretation thus requires cau-
tion, as these tests may not accurately reflect the in vivo hemostatic response. Additionally in humans there are normal biological variations that need to be factored in. In laboratory practice, the normal range is usually derived from disease-free subjects and defined as results that fall within two standard deviations above and below the mean for the normal population. Therefore, by definition, 5% of healthy subjects would have an abnormal coagulation test. In the absence of relevant clinical information, unnecessary further investigations may thus be prompted, generating delay, anxiety, cost, and perhaps unnecessary exposure to blood products. There are also technical variations in the method of performing the tests, as well as difficulties such as artifacts due to prolonged tourniquet placement, difficult or traumatic phlebotomy, inadequate sample volumes, heparin contamination, prolonged storage, and sampling from a line. Pathological states and clinically important diseases may be modified or masked by physiological responses. For example, factor VIII levels rise markedly in pregnancy and in response to physical stress and trauma. This results in a shortening of the PTT, which may mask the detection of mild hemophilia A and vWD.

**Recommended Assessment Strategies for Routine Patients**

The excellent review published by Samuel Rapaport in 1983, “Preoperative Hemostatic Evaluation: Which Tests, If Any?” continues to be the basis of our recommended approach. This approach to the general surgery patient would also be applicable to neurosurgical patients.

**Clinical Assessment**

Important clinical history questions to ask would include the following:

1. Is there a history of a bleeding disorder present? (This patient questionnaire has been adapted from Rapaport’s review and Koscielny et al’s review.)
   - Do you experience excess bleeding in your mouth/gums or frequent nose-bleeds without apparent reason?
   - Have you bled into a muscle or a joint? Have you ever had blood in your stool?
   - Do you develop large bruises or “blue spots” (hematoma) even in the absence of obvious injury/trauma? Have you bled excessively after small wounds? If so, how often do you have bleedings or “blue spots” (hematoma): one or two times a week or more often?
   - Did you ever have prolonged or grave bleedings during or after a tooth extraction?
   - What operations have you undergone, including minor procedures such as skin biopsies or colonoscopy/bronchoscopy with biopsies? Was there any bleeding, either immediate or delayed?
   - Do you have other medical problems? Is there a history of hepatic, renal, or hematologic disease? Have you ever required a transfusion of whole blood, red blood cells, platelets, plasma, or blood clotting factors? If so, please list the operation(s) or the reason(s).
3 Preoperative Coagulation Assessment

• What medications are you taking? Do you take anticoagulant medications? Have you taken aspirin or other pain relievers within the last 10 days? Do you take over-the-counter remedies, supplements, or alternative medicine (e.g., supplements/herbal preparations)?
• Do you have profuse menstrual bleeding? Do you have the impression that you have prolonged menstruation (> 7 days) or a high frequency of tampon change?

2. If there is a bleeding history, is the disorder familial or acquired?
• Age at presentation
• Duration of symptoms
• Response to previous hemostatic challenges
• Family history: Do any relatives have bleeding tendencies or experience excessive bleeding following surgery?

3. What type of bleeding disorder is present?

Table 3.1 summarizes clinical and physical examination features that are helpful in distinguishing platelet-type bleeding disorders from coagulation-type bleeding disorders.

4. Is there an underlying systemic disease? These would include:
• Liver disease
• Can cause thrombocytopenia (congestive splenomegaly)
• Increased fibrinolysis (deficiency of liver-derived factors that inhibit fibrinolysis, e.g., α₂-plasmin inhibitor)
• Dysfibrinogenemia
• Renal impairment
• Hypothyroidism
• Amyloidosis
• DIC: infection, trauma, tumors, toxins, obstetric complications, metabolic disorders
• Drug history
• Pregnancy

Table 3.1 Characteristics of Platelet- and Coagulation-Type Bleeding

<table>
<thead>
<tr>
<th>Platelet-Type bleeding</th>
<th>Coagulation-Type Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous</td>
<td>Large soft tissue bruises</td>
</tr>
<tr>
<td>Bleeding after minor cuts</td>
<td>Not usually</td>
</tr>
<tr>
<td>Small, superficial ecchymoses</td>
<td>Large, palpable ecchymoses</td>
</tr>
<tr>
<td>Petechiae and purpura</td>
<td>Hemarthrosis</td>
</tr>
<tr>
<td>Dominant family history</td>
<td>X-linked recessive history</td>
</tr>
<tr>
<td>Female predominance</td>
<td>Male predominance</td>
</tr>
<tr>
<td>Early bleeding/oozing, relatively milder to moderate</td>
<td>Delayed bleeding, relatively moderate to severe</td>
</tr>
</tbody>
</table>

Note: This table summarizes the features on history and physical exam that could help to distinguish bleeding arising from platelet deficiency/dysfunction versus defects in the coagulation cascade.
Fig. 3.1  This algorithm takes into consideration the limitations of clinical history and the various laboratory tests. This assessment strategy would be applicable to the pediatric and adult patient population. In general, neurosurgical cases would fall into the moderate- to high-risk category, given that minimal postoperative bleeding could be hazardous. The testing decision in most cases is often driven by the individual surgeon’s experience and expertise. Further testing of abnormal screening tests is outlined in other sections in this chapter. Hematology consultation should be obtained in uncertain cases. (PT, prothrombin time; PTT, partial thromboplastin time.)

Laboratory Assessment

Fig. 3.1 outlines an approach to the preoperative coagulation assessment strategies for routine neurosurgical patients.

Strategy for Handling Abnormal Values for Common Tests

Table 3.2 presents one approach to evaluating the screening tests of hemostasis (PT, PTT, platelet count) to generate a differential diagnosis of bleeding disorders and recommended subsequent testing. Fig. 3.2 summarizes a practical approach to evaluating a prolonged PTT.
Table 3.2  Interpretation of Hemostasis Screening Test Results in Patients with Bleeding Disorders and Suggested Subsequent Testing

<table>
<thead>
<tr>
<th>Platelet Count</th>
<th>PT</th>
<th>PTT</th>
<th>Frequency</th>
<th>Differential Diagnosis</th>
<th>Subsequent Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>N ↑ N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Factor VII deficiency (liver disease, vitamin K deficiency, warfarin)</td>
<td>Liver function panel, especially albumin.</td>
</tr>
<tr>
<td>N ↑ N</td>
<td>Rare</td>
<td>Factor VII inhibitor, inherited factor VII deficiency, DIC, superwarfarin</td>
<td>Factor VII deficiency, liver disease, vitamin K deficiency, warfarin, heparin, superwarfarin</td>
<td>Liver function panel, thrombin time, brodifacoum level</td>
<td></td>
</tr>
<tr>
<td>N ↑ N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Common 1. Deficiency of factors VIII, IX, XI 2. Heparin, hemophilia, vWD</td>
<td>Refer to Fig. 3.2</td>
</tr>
<tr>
<td>N ↑ ↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Common Vitamin K deficiency, liver disease, warfarin, heparin, superwarfarin</td>
<td>Liver function panel, thrombin time, brodifacoum level</td>
</tr>
<tr>
<td>N ↓ ↑ ↑</td>
<td>Rare</td>
<td>DIC, deficiency of factors X, V, prothrombin, fibrinogen, primary fibrinolysis</td>
<td>DIC, deficiency of factors X, V, prothrombin, fibrinogen, primary fibrinolysis</td>
<td>D-dimer, factors X, V, prothrombin, fibrinogen, FDP</td>
<td></td>
</tr>
<tr>
<td>↓ ↑ ↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Acute DIC, liver disease, heparin therapy</td>
<td>Liver function panel, D-dimer, fibrinogen, thrombin time</td>
</tr>
<tr>
<td>N ↑ N N</td>
<td>Common vWD, acquired platelet dysfunction (drugs, uremia)</td>
<td>vWD, acquired platelet dysfunction (drugs, uremia)</td>
<td>vWD, acquired platelet dysfunction (drugs, uremia)</td>
<td>vWD panel</td>
<td></td>
</tr>
<tr>
<td>N ↓ N N</td>
<td>Rare</td>
<td>Inherited platelet dysfunction, factor XIII deficiency, vascular disorders including hereditary hemorrhagic telangiectasia, mild factor deficiency, abnormal fibrinolysis</td>
<td>Inherited platelet dysfunction, factor XIII deficiency, vascular disorders including hereditary hemorrhagic telangiectasia, mild factor deficiency, abnormal fibrinolysis</td>
<td>Platelet aggregation studies, factor XIII, consider all factor assays</td>
<td></td>
</tr>
<tr>
<td>↓↓ N N</td>
<td>Increased platelet destruction, decreased platelet production, splenomegaly</td>
<td>Increased platelet destruction, decreased platelet production, splenomegaly</td>
<td>Increased platelet destruction, decreased platelet production, splenomegaly</td>
<td>Peripheral blood smear, consider bone marrow biopsy</td>
<td></td>
</tr>
<tr>
<td>↑↑ N N</td>
<td>Myeloproliferative disorders</td>
<td>Myeloproliferative disorders</td>
<td>Myeloproliferative disorders</td>
<td>Peripheral blood smear, bone marrow biopsy</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; vWD, von Willebrand disease.

Note: Differential diagnosis and suggested tests above assume that structural bleeding has been excluded. Warfarin and superwarfarin ingestion can be confirmed by assaying the four vitamin K–dependent factor levels: VII, X, IX, and prothrombin. Additionally, specific drug assays are available to evaluate warfarin and superwarfarin ingestion. Brodifacoum is the superwarfarin chemical responsible for the coagulopathy associated with rodenticide ingestion. Heparin presence in coagulation samples can be tested by using the thrombin time test. Platelet aggregation assays are only recommended to evaluate patients with possible inherited (not acquired) platelet dysfunction. Because the PT and PTT assays are screening tests, mild factor deficiency may not be detected by these assays, but abnormal hemostasis may still result in excessive surgical bleeding. Patients who are being evaluated for hemostatic disorders who have normal screening test results may require assay for all coagulation factor levels to achieve a diagnosis.
Conclusion

The important first step in detecting potential problems of hemostasis in patients about to undergo neurosurgery (or for that matter any surgery) would be a bleeding-tailored clinical history and physical examination. Screening tests cannot substitute for an inadequate history or physical examination. The neurosurgical literature is surprisingly devoid of well-designed, randomized trials that would enable definitive guidelines concerning routine preoperative coagulation testing. At present, it appears appropriate to perform a few inexpensive tests (platelet count, PTT, and possibly PT), knowing that their main usefulness is to provide baseline values for patients who will undergo a strong hemostatic challenge during neurosurgery. More specialized tests should be performed only as clinically indicated.

**KEY POINTS**

- Patient history, PT, PTT, and platelet count are clinically valuable when screening adult neurosurgery patients for risk of postoperative bleeding.
• Platelet count determination is clinically valuable for adult patients to rule out thrombocytopenia.
• Prothrombin time assesses the extrinsic and common pathways of clotting and is typically expressed in the INR format.
• Activated PTT tests the integrity of the intrinsic and common pathways of coagulation.
• Routine PT and PTT assessment are typically recommended to screen for problems of hemostasis in neurosurgery patients undergoing surgery, but the value of routine screening has not been validated in any randomized trials. Although PT and PTT assessment is recommended, it may provide, at most, baseline values.
• A DIC panel is not typically used but may be required if there are indicators that suggest uncontrolled coagulation or bleeding. The DIC panel includes D-dimer (increases), fibrinogen level (decreases), and FDPs, which increase. Platelet count also decreases.
• Coagulation screening tests can be meaningfully interpreted only with the knowledge of their limitations and the relevant clinical situation.

REVIEW QUESTIONS

1. A systematic patient history concerning operative bleeding risk should include the following questions:
   A. Does bleeding from mouth/gums and frequent nosebleeds occur?
   B. Has excessive bleeding ever occurred after surgery?
   C. Does bruising occur in the absence of obvious trauma?
   D. Is there a history of joint pain?
   E. Is there an allergy to aspirin?

2. A systematic patient drug history concerning operative bleeding risk should include questions regarding:
   A. Aspirin
   B. Acetaminophen
   C. Nonsteroidal anti-inflammatory drugs
   D. Corticosteroids
   E. Warfarin

3. A systematic patient history concerning operative bleeding risk should include questions regarding:
   A. Family history of bleeding disorders
   B. Alcohol consumption
   C. Smoking history
   D. Vitamin and nutritional supplement usage
   E. Family history of diabetes mellitus

4. Which of the following disorders may have an effect on bleeding risk?
   A. Amyloidosis
   B. Liver disease
   C. Kidney disease
   D. Rheumatoid arthritis
   E. Raynaud’s disease
5. A preoperative platelet count:
   A. Is essential for all adult patients
   B. Is not required for a surgery where a transfusion is expected
   C. Provides a useful baseline for the postoperative state
   D. Determines whether thrombocytopenia is an issue
   E. Is not required for any pediatric patients

6. A preoperative PT and PTT:
   A. Are essential for all adult patients
   B. Are not required for a surgery where a transfusion is expected
   C. Provide a useful baseline for the postoperative state
   D. May be abnormal in up to 5% of health subjects
   E. Are not required for any pediatric patients

References


**ANSWER KEY**

1. A, B, and C
2. A, C, and E
3. A, B, and D
4. A, B, and C
5. C and D
6. C and D
Clinical Disorders of Coagulation and Platelet Function

Justin D. Thomas and George M. Rodgers

This chapter briefly summarizes disorders of bleeding and thrombosis, including both inherited and acquired etiologies. Acquired etiologies of bleeding and thrombosis are more common than the inherited forms.

Thrombosis

Thrombosis is the process of forming a blood clot within a blood vessel, thus obstructing the flow of blood through the circulatory system. Most commonly, presentations of thrombosis occur as deep venous thrombosis of the lower extremity with or without pulmonary embolism. The underlying cause can be classified as acquired or hereditary. Virchow’s triad proposes thrombosis to be a consequence of one or more of the following: alterations in blood flow, vascular endothelial injury, and alterations in the constituents of the blood. The discussion in this chapter focuses primarily on venous thromboembolism (VTE).

Overview of the Causes of Venous Thrombosis

Inherited Thrombophilia

Inherited thrombophilia is a genetic tendency for thrombosis, which typically presents in younger patients (< 50 years of age) and is usually recurrent in nature. The most frequent causes are the factor V Leiden and the prothrombin gene mutations, which account for about 40% of the cases. Table 4.1 summarizes the inherited states, their prevalence, and the associated increased risk for thrombosis.

The effects of anticoagulant therapy and the setting of an acute thrombosis may both confound the laboratory evaluation of thrombophilia. However, the DNA tests for the factor V Leiden and prothrombin gene mutations, and an amino acid level for homocysteine, are not affected by anticoagulation and can be ordered at any time without concern about an incorrect test result. Table 4.2 summarizes the other inherited thrombophilias and potential confounding factors, which may affect a correct laboratory result. Although an extensive laboratory evaluation may identify an inherited thrombophilia in over 50% of affected patients, the available data indicate that positive thrombophilia test results do not change how patients should be managed.1
Acquired Venous Thrombophilia

Predisposing conditions for acquired venous thrombosis include a prior thrombotic event, recent major surgery or hospitalization, presence of a central venous catheter, trauma, immobilization, malignancy, pregnancy, certain medications (tamoxifen, lenalidomide), myeloproliferative disorders, and antiphospholipid antibodies. Many patients presenting with an episode of VTE have multiple risk factors. This was confirmed in a 1999 population-based study of VTE in Worcester, Massachusetts, in which six medical characteristics were identified:

1. More than 48 hours of immobility in the preceding month (45% of patients)
2. Hospital admission in the past 3 months (39%)
3. Surgery in the past 3 months (34%)
4. Malignancy in the past 3 months (34%)
5. Infection in the past 3 months (34%)
6. Current hospitalization (26%)

Only 11% of the 587 episodes of VTE in this study had none of the six risk factors, whereas 36% had one or two and 53% had > 3 risk factors.

**Malignancy**

Cancer patients have an increased risk of thrombotic events due to tumor expression of procoagulants, such as tissue factor. Clinical VTE occurs in about 5% of cancer patients and in 12% of cancer patients with a central venous catheter.

**Surgery**

Thrombotic risk is greatly increased during and after surgery. Additional risk factors in this group include older age, previous VTE, the coexistence of malignancy or medical illness, inherited thrombophilia, longer procedures, anesthesia, and longer immobilization times. Thromboprophylaxis greatly reduces the incidence of symptomatic VTE in the immediate postoperative period. There continues to be a risk for subsequent VTE following discharge, especially in orthopedic patients who require longer thromboprophylaxis. Neurosurgical patients specifically have a high incidence of VTE as shown in a prospective study done in 2009. Using mechanical prophylaxis, five of 37 patients (13.5%) developed asymptomatic DVT confirmed by ultrasound. Of those five patients, three eventually had a pulmonary embolism, suggesting the need for additional pharmacological prophylaxis.

Thromboprophylactic management of the neurosurgical patient, with a high risk for both thrombosis and intracranial bleeds, was recently reviewed by Niemi and Armstrong. They concluded that thromboprophylaxis and bridging therapy should be tailored to the individual risks and the type of neurosurgery. The bleeding risk is minimized by allowing coagulation capacity to normalize preoperatively and by using reduced doses of low molecular weight heparin (LMWH) starting relatively late after neurosurgery.

**Trauma**

Major trauma significantly increases the risk of VTE. One study detected thrombi in 54% of patients with major head trauma, 61% of patients with pelvic fractures, 77% of patients with tibial fractures, and 80% of patients with a femoral neck fracture. Increased VTE risk has also been associated with a minor injury occurring in the preceding 3 to 4 weeks.

**Pregnancy**

Estimates of the age-adjusted incidence of VTE range from 5 to 50 times higher in pregnant versus nonpregnant women and is likely due to obstruction of venous return from the enlarged uterus as well as the hypercoagulable state associated with pregnancy.
Drugs

Oral and transdermal contraceptives increase the risk of VTE within 4 months of the initiation of therapy. The Women's Health Initiative along with the Heart and Estrogen/progestin Replacement Study (HERS) have also shown a twofold increase in VTE associated with hormone replacement therapy, which appeared greatest in the first year of treatment.

Immobilization

This category encompasses patients with recent hospitalizations; patients on bed rest; deconditioned elderly patients; patients with stroke, heart failure, or recent myocardial infarction; as well as patients who have undergone recent extended travel.

Antiphospholipid Antibodies

The antiphospholipid syndrome is characterized by the presence of antibodies directed against plasma proteins bound to anionic phospholipids in patients who present with arterial or venous thrombosis, complications of pregnancy, recurrent fetal loss, or thrombocytopenia. Etiologies may be either primary (idiopathic) or secondary due to autoimmune syndromes such as systemic lupus erythematosus, malignancy, infections, or drug reactions. Although a prolonged partial thromboplastin time (PTT) that does not correct with mixing with normal plasma may be seen, optimal testing for antiphospholipid antibodies includes assays for the lupus anticoagulant, immunoglobulin (Ig)G and IgM anticardiolipin antibodies, and IgG and IgM antibodies to β2-glycoprotein-1. In contrast to test results indicating inherited thrombophilia, which usually do not change patient management, positive results for antiphospholipid antibody tests do change the duration of treatment. Patients with antiphospholipid syndrome should receive therapeutic anticoagulation for as long as positive antiphospholipid antibody test results persist.\textsuperscript{11}

Myeloproliferative Neoplasms and Paroxysmal Nocturnal Hemoglobinuria

The chronic myeloproliferative neoplasms, particularly polycythemia vera (PV) and essential thrombocytopenia, are characterized by thrombotic complications, both arterial and venous. Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal bone marrow disorder that results in intravascular hemolysis with episodes of hemoglobinuria and occasional leukopenia or thrombocytopenia. PNH is associated with an increased incidence of venous or arterial thrombosis.

Renal Disease

Chronic renal disease, nephrotic syndrome, and renal transplantation have all been reported to have an increased incidence of VTE. Patients with stage III/IV chronic renal disease have a relative VTE risk of 1.7 compared with patients with normal renal function.\textsuperscript{12}
Contrary to the popular belief that auto-anticoagulation occurs with liver disease and cirrhosis, a retrospective cohort of 190 hospitalized patients with chronic liver disease showed 12 (6.3%) developed VTE. The mechanism may be a result of acquired protein C and S deficiency.

**Hyperviscosity**

Thrombosis can be a manifestation of diseases associated with serum hyperviscosity (Waldenström macroglobulinemia or multiple myeloma), an increased number of red blood cells (PV), or a decrease in deformability of red cells as seen in sickle cell disease. Presenting symptoms include bleeding due to platelet dysfunction, visual disturbances, neurologic defects, deep venous thrombosis, pulmonary embolism, and portal and hepatic venous thrombosis.

**Hyperhomocysteinemia**

This disorder may occur either as a genetic or an acquired abnormality. The genetic disorder is associated with homozygosity for the thermolabile mutant of the enzyme methylenetetrahydrofolate reductase, or heterozygosity or homozygosity for cystathionine β-synthase. Homocysteine concentrations can also be elevated in acquired disorders such as vitamin B₆, vitamin B₁₂, and folic acid deficiencies.

**Bleeding Disorders**

**Platelet Disorders**

Disorders of platelet function include a common inherited bleeding disorder (von Willebrand disease), several rare congenital disorders, as well as a myriad of common acquired conditions. Platelet-type bleeding symptoms include easy bruising, mucocutaneous bleeding, and menorrhagia.

Acquired platelet disorders are more common, with the most likely etiology being secondary to therapeutic antiplatelet agents. These agents include aspirin, other nonaspirin nonsteroidal anti-inflammatory drugs, dipyridamole, clopidogrel, and other glycoprotein (GP)IIb/IIIa receptor antagonists, including abciximab and eptifibatide. Another acquired platelet function disorder is liver disease, which can induce both qualitative and quantitative platelet defects in not only chronic disease but also acute liver damage. Cardiopulmonary bypass also can cause significant platelet dysfunction due to numerous factors, including the interaction of platelets with the nonphysiologic surface components of the bypass membrane. Hypothermia during bypass, complement activation, release of cytokines, and thrombin generation may also contribute. Uremia associated with chronic renal failure has also been associated with increased clinical bleeding due to intrinsic platelet metabolic defects, and defects in platelet-endothelial interactions. Of course, malignancy and clonal disorders as well as thrombocytopenia secondary to several underlying disorders all may contribute to an increased propensity to bleed excessively.

Inherited disorders of platelet function include the most common bleeding disorder, von Willebrand disease (vWD), as well as the uncommon qualitative platelet
disorders Bernard-Soulier and Glanzmann thrombasthenia, and disorders of platelet secretion and signal transduction including storage pool diseases, Hermansky-Pudlak syndrome, and Quebec platelet disorder. This category also includes signal transduction defects as well as abnormalities in arachidonic acid pathways and thromboxane A₂ synthesis. Defects in cytoskeletal regulation include Wiskott-Aldrich syndrome. Finally, Scott’s syndrome is characterized by a defect in platelet procoagulant function.

Coagulation-Type Bleeding Disorders: Acquired and Hereditary

Coagulation-type bleeding symptoms include deep soft tissue hematomas, visceral bleeding, and hemarthrosis. The most common acquired coagulation disorder is associated with anticoagulant drugs, for example antithrombin inhibitors such as heparin products, factor Xa inhibitors such as fondaparinux, and the vitamin K antagonists such as warfarin. Liver disease and vitamin K deficiency from poor or inadequate nutrition can also lead to a coagulopathy. Acquired inhibitors, due to antibodies, can also either inhibit the activity or increase the clearance of a clotting factor, making a patient more likely to bleed. The most common antibodies that affect clotting factor activity are directed against factor VIII, in a disorder known as acquired hemophilia A. This condition can be seen in postpartum women, rheumatologic disease, and certain solid malignancies. Other inhibitors include antibodies directed against other coagulation proteins.

Inherited or congenital disorders of coagulation proteins include vWD, hemophilia A (factor VIII deficiency), and hemophilia B (factor IX deficiency), as well as less common factor deficiencies, such as fibrinogen, prothrombin, and factors V, VII, X, XI, and XIII. Laboratory evaluation of coagulation disorders is discussed in Chapter 3.

KEY POINTS

• Disorders of bleeding and thrombosis can be categorized as either acquired or inherited.
• Clinical history and appropriate laboratory testing determine whether a patient has either a platelet-type or a coagulation-type bleeding disorder.
• Inherited thrombophilia typically presents in patients younger than 50 years of age and is usually recurrent in nature.
• Acquired thrombosis is more common than the inherited thrombophilias, and may be seen in patients with any or all of the following: alterations in blood flow (stasis), vascular endothelial injury, and alterations in the constituents of the blood (hypercoagulability).
REVIEW QUESTIONS

In the following case examples, one or more answers may be correct.

Case 1

Mrs. B.C. is a 65-year-old Hispanic woman currently being evaluated preoperatively for a planned laminectomy for severe spinal stenosis. Her clinical history is significant for bleeding after a wisdom tooth extraction at age 21. She denies any other surgeries, but notes menorrhagia with previous ovulation, along with mild to moderate bleeding after minor cuts. After further discussion, you discover a possible dominant inheritance pattern of bleeding (males and females being affected in several generations). A complete blood count (CBC) and platelet counts are within normal limits.

1. Does the history point more to a platelet-type of coagulation-type bleeding disorder?
   A. Coagulation type, most likely inherited
   B. Coagulation type, most likely acquired
   C. Platelet type, most likely inherited
   D. Platelet type, most likely acquired

2. What are the two most likely clinical disorders in your differential?
   A. vWD
   B. Inherited platelet dysfunction
   C. Thrombocythemia
   D. Thrombocytopenia

3. What acquired disorders would appear to be less likely?
   A. Liver, renal dysfunction
   B. Medication-induced platelet dysfunction
   C. Long-standing myeloproliferative disorder

4. What are the appropriate laboratory evaluations?
   A. CBC to exclude thrombocytopenia and myeloproliferative disorder
   B. Thrombin level and D-dimer
   C. Von Willebrand testing

Case 2

Mr. J.F. is a 45 year-old man with no significant past medical history who recently experienced a subdural hematoma requiring evacuation. His surgery was uneventful. However, on postoperative day 21, he develops erythema, swelling, and pain in his lower right extremity. He is seen in a neurosurgery clinic where an ultrasound is obtained, which confirms a deep venous thrombosis. Upon further questioning, it is discovered that his father and uncle both experienced unprovoked thrombosis.

1. At this point in his clinical care, is it reasonable to evaluate this patient for an inherited hypercoagulable disorder?
   A. No
   B. Yes
2. If the patient requests an inherited thrombophilic evaluation, which tests should be sent to the lab before anticoagulation?
   A. Factor V Leiden
   B. Prothrombin gene mutation
   C. Homocysteine level as these tests will not be affected by acute thrombosis
   D. Antithrombin
   E. Protein C
   F. Protein S

3. Which tests should be sent to the lab during heparin or oral anticoagulation?
   A. Factor V Leiden
   B. Prothrombin gene mutation
   C. Homocysteine level as these tests will not be affected by acute thrombosis
   D. Antithrombin
   E. Protein C
   F. Protein S

4. Which tests should be sent to the lab after discontinuation of oral anticoagulation (1 month)?
   A. Factor V Leiden
   B. Prothrombin gene mutation
   C. Homocysteine level as these tests will not be affected by acute thrombosis
   D. Antithrombin
   E. Protein C
   F. Protein S

References

**ANSWER KEY**

**Case 1**

1. C
2. A and B
3. A, B, and C
4. A and C (von Willebrand testing includes von Willebrand factor multimers, factor VII activity, von Willebrand factor antigen, and ristocetin cofactor activity; if they are normal, then perform platelet aggregation testing)

**Case 2**

1. A (this particular event could be explained simply due to immobility during his recent surgery and recovery; also, there are no clinical data to support the idea that identifying an inherited thrombophilia would change patient management)
2. A to C (these tests are not affected by acute thrombosis)
3. A to C
4. D to F
Drugs Affecting Coagulation and Platelet Function
Amir Assel and Kenneth B. Hymes

The management of bleeding in the perioperative setting is important to any surgeon, and the use of anticoagulation and antiplatelet therapy for a wide variety of clinical conditions makes this a more critical problem. Many patients in need of urgent and elective neurosurgical procedures have received anticoagulant medications, and the reversal of their effect is necessary to reduce the risk of hemorrhage. Interruption of therapy and its management in the perioperative setting is not straightforward. This chapter reviews mechanisms of actions of the standard and novel anticoagulant medications and provides rationales for the management of anticoagulation in the preoperative setting.

Oral anticoagulation therapy (OAC) is indicated for a variety of disorders. It is used for stroke prevention in patients with atrial fibrillation or left ventricular thrombi, and in those who have received mechanical valves. It is also indicated for the treatment of deep venous thrombosis (DVT), pulmonary embolus, and a variety of acquired and genetic hypercoagulable conditions. Antiplatelet therapy is used for the primary and secondary prevention of stroke and coronary artery disease. It is also used for prevention of in-stent thrombosis in patients who receive percutaneous intervention for acute coronary syndromes with bare metal stents or drug-eluting stents. Patients with atrial fibrillation are also at risk for acute coronary syndrome. These patients are routinely discharged on “triple therapy,” which is the use of two antiplatelet agents along with OAC. Finally, low-dose anticoagulation is also indicated for DVT prophylaxis in hospitalized patients. The increased use of such therapies poses management dilemmas in patients undergoing neurosurgery.

Vitamin K Antagonists

The most commonly used vitamin K antagonist (VKA) is warfarin.1 VKAs exert their anticoagulant effect by interfering with the synthesis of the vitamin K–dependent clotting factors II, VII, IX, and X.2 VKAs inhibit the recycling of vitamin K epoxide to its reduced form. The reduced form of vitamin K is necessary for the γ-carboxylation of glutamate residues in the N-terminal region of the vitamin K–dependent coagulation factors. γ-Carboxylation is necessary for calcium binding, which creates a conformational change in the protein structure and promotes the binding of vitamin K–dependent factors to cofactors on phospholipid surfaces, thereby exerting their coagulant effect.

When the anticoagulant effect of VKA must be reversed, the urgency of the clinical situation (elective versus emergency surgery), the half-life of the drug, and the half-life of the vitamin K–dependent coagulation factors need to be considered.
Outpatient Management of Vitamin K Antagonist Reversal

The American College of Chest Physicians (ACCP) guidelines on the pharmacology and outpatient management of VKA delineate management options based on the international normalized ratio (INR) value and the presence of bleeding. If the INR is supra-therapeutic but < 5, a dose can be withheld or adjusted, the INR can be monitored more frequently, and therapy can be resumed when the INR is in the therapeutic range. If the INR is ≥ 5 but < 9, then one of more doses can be withheld, the INR monitored more frequently, and therapy can be resumed at an adjusted dose once the INR is in the therapeutic range. Alternatively, the guidelines call for the use of oral vitamin K in the following manner: omitting a dose of warfarin and administering 1 to 2.5 mg of vitamin K if the patient is at risk of bleeding, or administering 5 mg or less of vitamin K if the patient requires urgent surgery and rapid reversal with additional doses if the INR is still high after 24 hours. If the INR is > 9, and the patient has no serious bleeding, the guidelines call for withholding therapy and administering a higher dose of vitamin K (2.5 to 5 mg) with more frequent INR monitoring. In patients with serious bleeding and elevated INR, regardless of the magnitude of elevation, the guidelines recommend withholding warfarin, and administering 10 mg of vitamin K by slow intravenous infusion, along with fresh frozen plasma, prothrombin complex concentrate (PCC), or recombinant factor VIIa depending on the urgency of the situation. Vitamin K dosing can be repeated as necessary. These recommendations are summarized in Table 5.1.

Emergent Reversal of Vitamin K Antagonist Effect

Vitamin K

Oral vitamin K has excellent bioavailability, but intravenous administration has the advantage of more rapid onset of action, and there is variability in the efficacy of the various oral preparations of vitamin K. Intravenous vitamin K has a more rapid onset of action than does subcutaneous vitamin K, although the later was just as efficacious at 72 hours. Furthermore, subcutaneous vitamin K has unpredictable bioavailability and clinical efficacy. Intravenous vitamin K was noted to be faster at 2 hours when the INR was > 10 but of equal efficacy when the INR was between 6 and 10. Thus intravenous vitamin K would be the route of choice if there is active hemorrhage; however, it is not recommended as a sole agent if more rapid correction of the INR is needed.

Intravenous vitamin K must be infused slowly to prevent an anaphylactoid reaction. This reaction, although potentially fatal, remains rare (an estimated 3 cases per 100,000), and the benefits of hemostasis outweigh the risk, particularly in the setting of neurosurgical bleeding. The recommended infusion rate is 1 mg per minute, although lower rates, as low as 1 mg per hour, have been suggested. Common practice is to dilute vitamin K in 50 mL of intravenous fluid and administer it over 30 minutes.

The onset of the effect of vitamin K depends on the half-life of the coagulation factors. Factor VII, which has a half-life of 5 hours, is repleted most rapidly, whereas the level of factors II, IX, and X, with half-lives of 65, 25, and 40 hours, respectively, will not be restored to hemostatic levels for 24 to 72 hours. Consequently, replace-
ment of coagulation factors with fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), or recombinant factor VIIa (rFVIIa) is necessary for rapid reversal of the effect of VKAs.

**Table 5.1  American College of Chest Physicians (ACCP) Guidelines on the Pharmacology and Management of Patients Receiving Vitamin K Antagonists**

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Intervention</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin INR &lt; 5</td>
<td>Hold dose</td>
<td>1,2</td>
</tr>
<tr>
<td>Warfarin INR &lt; 5–9</td>
<td>Hold dose</td>
<td>1,2</td>
</tr>
<tr>
<td></td>
<td>Oral vitamin K 1–2.5 mg</td>
<td></td>
</tr>
<tr>
<td>Warfarin INR &gt; 9, no hemorrhage</td>
<td>Hold dose</td>
<td>1,2</td>
</tr>
<tr>
<td></td>
<td>Oral vitamin K 2.5–5 mg</td>
<td></td>
</tr>
<tr>
<td>Warfarin and hemorrhage</td>
<td>Hold dose</td>
<td>1,2</td>
</tr>
<tr>
<td></td>
<td>IV vitamin K 10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Factor replacement (FFP, PCC or rVIIa)</td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin supratherapeutic PTT</td>
<td>Interrupt heparin infusion for 2–4 hours; resume</td>
<td>26,35</td>
</tr>
<tr>
<td></td>
<td>at reduced dose</td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin supratherapeutic PTT and hemorrhage</td>
<td>Interrupt heparin infusion for 2–4 hours; resume at reduced dose; protamine</td>
<td>35,36</td>
</tr>
<tr>
<td>Low molecular weight heparin and hemorrhage</td>
<td>Hold dose</td>
<td>35,36</td>
</tr>
<tr>
<td></td>
<td>Protamine (partially effective; PCC or rVIIa)</td>
<td></td>
</tr>
<tr>
<td>Heparin pentasaccharide</td>
<td>Hold dose</td>
<td>35,36,39</td>
</tr>
<tr>
<td></td>
<td>PCC or rVIIa</td>
<td></td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>Hold dose</td>
<td>41,43</td>
</tr>
<tr>
<td></td>
<td>PCC or rVIIa (no evidence of efficacy)</td>
<td></td>
</tr>
<tr>
<td>Oral Xa Inhibitors</td>
<td>Hold dose</td>
<td>42,43</td>
</tr>
<tr>
<td></td>
<td>PCC or rVIIa</td>
<td></td>
</tr>
</tbody>
</table>

**Fresh Frozen Plasma**

Warfarin reversal is the most common indication for the use of FFP in the United States. The widely used dose of FFP is 15 mL/kg. There are data to suggest that this dose may be insufficient to correct the coagulopathy, as factor IX levels may remain low. Dosages up to 40 mL/kg have been recommended, and patients may require a total volume of 2 L. The disadvantage of the use of large volumes of FFP is the risk of fluid overload; in addition, each unit of FFP expands the plasma volume and reduces the effective increase in coagulation factor activity. Earlier administration of FFP increases the likelihood of correction of coagulopathy within 24 hours. A reduction in mortality and hemorrhage progression can be achieved by...
the implementation of institutional protocols aimed at rapid diagnosis and infusion of FFP. Nevertheless, several studies report difficulties with FFP administration primarily due to the time needed to prepare the product and the risk of fluid overload, as many patients receiving OAC may have heart disease. As with any blood-derived product, FFP entails the risk of transmission of infectious agents. With these difficulties in mind, alternative therapies to FFP, such as PCCs and rVIIa, have been studied and have made their way into treatment guidelines.

Prothrombin Complex Concentrates

The PCCs are plasma-derived products that contain factors II, V, VII, and IX. Their Food and Drug Administration (FDA)-approved indication is for the treatment of factor IX deficiency in hemophilia B, and their labeling cites only the measurement of factor IX activity. The formulations vary in their coagulation factor composition; most products available in the United States have much lower amounts of factor VII activity than factor IX activity. The available PCCs are summarized by Schulman and Bijsterveld. These products are derived from pooled human plasma; thus, they entail the risk of transmission of infectious agents. Consequently, all of these products are treated to eliminate viruses. The factor concentration is about 25 times higher than that of FFP; thus, much smaller volumes of these products are necessary for effective treatment. The ACCP guidelines on the pharmacology and management of VKAs emphasize that “immediate and full correction [of coagulopathy] can only be achieved by the use of factor concentrates” due to the limitation associated with FFP as stated above.

A dose of 500 IU of PCC for VKA reversal, based on factor IX activity, has been recommended along with vitamin K in patients with an INR of ≤ 5. INR reversal was achieved in ≤ 10 minutes with a sustained effect at 12 to 24 hours. Higher doses, up to 1500 IU, may be required for patients with an INR > 5, or weight-based dosing at 26 IU/kg has been suggested. Dosing can also be calculated using the patient’s INR, target INR, and body weight. The factor levels can be roughly estimated based on the INR, and the difference between starting and target coagulation factor levels calculated. The difference is multiplied by the patient’s weight in kilograms, and the product is the number of units of coagulation factor concentrate or milliliters of FFP that need to be administered. This formula overestimates the amount of replacement necessary, because the coagulation factors are distributed in the plasma volume, which is about 70% of the body weight.

Prothrombin complex concentrate carries the risk of both venous and arterial thromboses. High doses of PCC may increase the risk of thromboembolism due to the accumulation of coagulation factors with longer half-lives (factors II and X) and the presence of activated coagulation factors in the product. The risk varies, as some formulations contain different levels of activated coagulation factors, and some products have included protein C and S to provide a balance between procoagulant and anticoagulant proteins and antithrombin and heparin to inhibit the in vivo activation of clotting factors.

The use of PCCs in the setting of intracerebral hemorrhage (ICH) has been studied, and this treatment has a superior reversal of anticoagulant effect with respect to correction of the INR compared with FFP and vitamin K or vitamin K alone. Clinical outcomes include a decrease in hematoma size and in perioperative bleeding. INR reversal was achieved in 84% of patients who received PCC, 39% of patients who received FFP, and 0% of the patients who received vitamin K alone. There was,
however, no statistically significant effect upon clinical outcome. Several of the patients in each of these studies developed thrombotic complications. Statistical analysis of data did not permit identification of the increased risk due to the treatment with PCCs. All of these studies were retrospective or the treatment group was compared with historical controls. These findings remain to be confirmed by randomized controlled study.\textsuperscript{17–21}

**Recombinant Factor VIIa**

Recombinant factor VIIa (rFVIIa) was initially used to treat bleeding episodes in patients with hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency).\textsuperscript{23} In the United States it is FDA approved for use in hemophilia A and B bleeding episodes, prophylaxis of bleeding in the surgical setting in those patients, in patients with factor VII deficiency, and in patients who have acquired factor VIII or IX deficiencies due to inhibitors. It is widely used off-label in a variety of scenarios that involve surgical bleeding of uncontrolled bleeding. In regard to ICH, rFVIIa has been studied in the settings of traumatic brain injuries, spontaneous ICH, and anticoagulant-associated ICH.

In the setting of traumatic ICH, the efficacy of rFVIIa was studied in patients with traumatic brain injuries who were not anticoagulated in a randomized controlled trial.\textsuperscript{24} Patients were randomized to placebo or to escalating doses of rFVIIa ranging from 40 to 200 µg/kg. There was no significant difference in mortality or adverse event, but there was a trend toward decreased hematoma volume in those receiving a dose of 80 µg/kg or higher. There was also a trend toward increased rate of DVTs.

In the setting of spontaneous ICH, rFVIIa was studied by Mayer et al\textsuperscript{25–28} in four randomized controlled trials. In the larger of the two dose-escalation trials, 399 patients with ICH were randomized to either placebo or escalating doses of rFVIIa (40, 80, or 160 µg/kg). Patients with oral anticoagulant use were excluded. Patients treated with rFVIIa had decreased hematoma expansion and improved mortality and functional outcomes at 90 days. The treatment arm, though, experienced a higher rate of thromboembolic events (7% compared with 2% in the placebo arm). In a phase 3 trial conducted by the same group,\textsuperscript{28} 841 patients were randomized to receive placebo or 20 or 80 µg/kg of rFVIIa. Again, decreased hematoma expansion was noted, but there was no difference in mortality or incidence of poor clinical outcomes. There was an increase in the incidence of arterial thromboembolic events in the group treated with 80 µg/kg. Hence, rFVIIa has not been approved for use in spontaneous ICH.

The efficacy of rFVIIa in reversing anticoagulation has been studied. In a case series of 13 patients, rFVIIa was given to patients receiving oral anticoagulation who had clinically significant bleeding or who had excessively high INR (> 10).\textsuperscript{29} Doses varied from 15 to 90 µg/kg. In all patients, the INR was immediately reduced. Factor activities were measured, and only factor VII was increased. In a prospective study of patient receiving oral anticoagulation with an acute major bleeding event, rFVIIa was given at a fixed dose of 1.2 mg for reversal of anticoagulation.\textsuperscript{30} Mean INR was significantly reduced and a favorable hemostatic effect was noted in 14 of the 16 patients in the trial. Some patients, however, received vitamin K and FFP.

In a case series of patients with central nervous system hemorrhages, rFVIIa was given in conjunction with FFP.\textsuperscript{31} Each patient received 1.2 mg of rFVIIa. All had normalization of their INR within 2 hours. Surgical blood loss was ≤ 100 mL.
Another similar case series reported the use of rFVIIa in addition to FFP and vitamin K (dose range 15–90 µg/kg). The INR decreased from a mean of 2.7 to 1.08. In a retrospective, controlled study of warfarin-associated ICH, 12 patients who received rFVIIa in addition to FFP and vitamin K were compared with 15 who did not.32 Mortality was higher in the rFVIIa group, but these patients had worse Glasgow Coma Scale scores at presentation. Time to correction of INR was earlier in the rFVIIa group (8.8 versus 32.2 hours), and the volume of FFP was almost half. One patient in the rFVIIa group developed disseminated intravascular coagulation, but this patient had renal disease and had received multiple doses of rFVIIa. In another retrospective study, the efficacy of an emergency department protocol to administer 1.2 mg of rFVIIa to patients with warfarin use and traumatic ICH was studied.33 Twenty patients were included in each cohort. Time to normalization of INR was earlier in the rFVIIa cohort (4.8 versus 12.5 hours). No difference in mortality or incidence of thrombotic events was noted.

In light of the evidence above, rFVIIa seems to play no major role in the management of ICH, either related or unrelated to warfarin treatment, and its use should be reserved for situations in which other therapies have failed.

Heparins

Heparins are routinely used in acute coronary syndromes and for treatment and prophylaxis of DVT. They are also used as bridging therapy for patients with prothrombotic heart valves and high-risk atrial fibrillation. Treatment in acute coronary syndromes is usually short term, only during acute hospitalization. For DVT, where anticoagulation is usually for longer durations, heparins are often used until the therapeutic effect of VKAs is achieved. The wide use of these drugs often impacts the perioperative management of neurosurgical patients.34

Unfractionated Heparin

Unfractionated heparin (UFH) is a heterogeneous mixture of sulfated glycosaminoglycans derived from porcine intestines.35 It exerts its anticoagulant effect by binding to antithrombin via a high-affinity pentasaccharide present in about a third of heparin molecules. The heparin–antithrombin complex has a high affinity for factor Xa, and the inactivation of this coagulation factor provides the majority of the anticoagulant activity of heparin. Larger molecules of heparin can also inactivate thrombin (factor IIa) and provide additional anticoagulant effect.

Unfractionated heparin can be used intravenously for full-dose systemic anticoagulation or, at lower doses, for DVT prophylaxis. The therapeutic effect of intravenous UFH is monitored with the partial thromboplastin time (PTT). In patients receiving UFH who experience life-threatening bleeding, as in the case of ICH, the drug must be promptly withheld and its therapeutic effect reversed. Because the half-life of intravenous UFH is short (60–90 minutes), interruption of the dosing is the most common means to treat bleeding episodes caused by this medication.

More immediate correction of heparin-induced coagulopathy can be achieved by treatment with protamine. Protamine sulfate is a basic protein derived from fish sperm and can rapidly reverse heparin by binding to it and forming a stable salt36; 1 mg of protamine sulfate will neutralize approximately 100 U of UFH. The dose of protamine is calculated from the amount of UFH given in the previous 3 hours.
Thus, for a dose of 1,200 U per hour of UFH, 12 mg of protamine will reverse the
dose of the past hour, 6 mg for the hour before that, and 3 mg for the hour before
that, for a total dose of 21 mg. The maximum dose of protamine is 50 mg, and it
has a short half-life of about 7 minutes. The effect of protamine can be monitored
with the PTT. Severe side effects of protamine can include bradycardia and hypo-
tension, which can be avoided by slow infusion. Patients who may have received
protamine-containing insulin, undergone vasectomy, or have a sensitivity to fish
may have preformed antibodies to protamine and are at risk of allergic reactions
including anaphylaxis. Such patients may be pretreated with corticosteroids and
antihistamines.

Low Molecular Weight Heparins

Low molecular weight heparins (LMWHs) are synthesized from UFH by chemical
or enzymatic depolymerization. These LMWHs include enoxaparin, dalteparin,
danaparoid sodium, nadroparin, and tinzaparin. They have a greater inhibition of
factor Xa compared with thrombin. They similarly bind to thrombin by a pentasac-
charide chain present in less than a third of all molecules. LMWH is typically ad-
ministered in a weight-based dose and has a renal clearance, so it should be given
with caution to patients with creatinine clearances of < 30 mL/min. The therapeu-
tic effect of LMWH can be monitored by obtaining the anti-Xa level with a therapeu-
tic level of 0.4 to 0.8 units/mL. Routine monitoring of the anti-Xa level is usually
not required; however, it may be necessary during pregnancy (where the plasma
volume increases over time) or in patients with borderline renal function.

Heparin Pentasaccharide

Heparin pentasaccharide (fondaparinux; trade name Arixtra, Glaxo Smith Kline,
Parsippany, NJ) is a synthetic analogue of the antithrombin-binding pentasaccha-
ride motif of heparins. It selectively inhibits factor Xa and has a longer half-life,
allowing for once daily dosing. Fondaparinux has been studied in the treatment
and prophylaxis of DVT and in the treatment of acute coronary syndromes. It has
a safety profile similar to that of unfractionated heparin and LMWH with respect
to bleeding complications. It is contraindicated in patients with creatinine clear-
ance < 30 mL/min. It has also been used safely in patients with heparin-induced
thrombocytopenia. The dose for DVT prophylaxis and acute coronary syndromes
is 2.5 mg. A higher dose of 7.5 mg is used for DVT treatment. It can be weight ad-
justed, with 5 mg used in patients with a body weight of < 50 kg and 10 mg in
patients with a body weight of > 100 kg.

Unlike UFH, the half-lives of LMWHs and fondaparinux are long (8–12 hours
and 17–21 hours, respectively). Should a patient experience bleeding while being
treated with these agents, interruption of dosing will not lead to a rapid decline in
anticoagulant activity.

Protamine sulfate can be given to reverse the anticoagulant effect of LMWH,
but it is not completely effective. Protamine primarily binds to the larger heparin
molecules and reverses the antithrombin effect; it has minimal impact on the
anti-Xa effect. The ACCP guidelines recommend using 1 mg of protamine for each
100 anti-Xa units of LMWH. For enoxaparin, 1 mg is equivalent to ~100 anti-Xa
units.
Fondaparinux has no approved antidote. The anticoagulant effect cannot be inhibited by protamine. Because its mechanism of action is to antagonize factor Xa, generation of excess Xa by treatment with rFVIIa has been investigated. In a study of 16 healthy volunteers, subjects were randomized to receive 10 mg of fondaparinux and 90 µg/kg of rFVIIa ($n = 8$), fondaparinux and placebo ($n = 4$), or placebo and rFVIIa ($n = 4$). Thrombin generation and activity were measured. Fondaparinux doubled the thrombin generation time, decreased the thrombin potential, and decreased the prothrombin activation peptide fragment 1 + 2 (F 1 + 2). All of these measures were reversed with rFVIIa. Furthermore, the modestly slightly increased activated partial thromboplastin time (aPTT) and prothrombin time (PT) after fondaparinux administration was normalized by rFVIIa. There are no clinical studies examining the role rFVIIa in reversing fondaparinux in the setting of bleeding.

**Oral Direct Xa Inhibitors**

Oral Xa inhibitors are small synthetic molecules that bind to factor Xa and inhibit its enzymatic function. Rivaroxaban has been approved by the FDA for DVT prophylaxis after orthopedic surgery in a dose of 10 mg daily and for prevention of arterial embolization in patients with nonvalvular atrial fibrillation at a dose of 20 mg daily. It was shown to be noninferior to enoxaparin for treatment of DVT and was equally effective as warfarin in atrial fibrillation in the ROCKET AF trial (Rivaroxaban once daily, Oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation). As with fondaparinux, there is no antidote for rivaroxaban, but rFVIIa has been shown to partially reverse rivaroxaban-induced prolongation of bleeding time, PT, and thrombin generation in animal models.

**Direct Thrombin Inhibitors**

Direct thrombin inhibitors (DTIs) are synthetic molecules that inhibit soluble and fibrin-bound thrombin. There are four FDA-approved DTIs that are given intravenously: lepirudin, desirudin, bivalirudin, and argatroban. An oral alternative is available; the one furthest along in development is dabigatran.

Lepirudin can be used in the management of heparin-induced thrombocytopenia (HIT). It is given with or without a bolus of 0.4 mg/kg followed by an infusion at a rate of 0.15 mg/kg/h. Drug may accumulate due to the formation of antibodies that delay renal clearance, so the dose must be adjusted based on aPTT values.

Desirudin is FDA approved for DVT prophylaxis in patients undergoing hip surgery. It is given subcutaneously at a dose of 15 mg twice daily and was shown to be superior to unfractionated heparin and enoxaparin. In severe renal impairment, dose reduction and monitoring of aPTT has been recommended.

Bivalirudin is a synthetic molecule that reversibly binds to thrombin that accounts for its better safety profile with respect to bleeding compared with lepirudin and desirudin. It has a short half-life of 25 minutes, and therapeutic effect can be reached within 5 minutes. Its use is limited to the percutaneous coronary intervention setting for acute coronary syndromes. It is contraindicated in patients with severe renal impairment.

Argatroban also binds reversibly to thrombin. It is approved in the United States for use in patients with HIT. It is given as an intravenous infusion at a rate of
2 µg/kg/h. It is cleared by the liver, so dose adjustments are not needed for patients with renal failure. The therapeutic effect can be monitored by aPTT. It also prolongs the PT, so when used in conjunction with warfarin as a bridging therapy, higher INR values are needed, typically > 4.

Dabigatran is an oral DTI. It has shown promise in replacing VKA. It is currently approved in Canada and Europe for the prophylaxis of DVT in patients undergoing total hip replacements. It is also approved in the United States for stroke prevention in atrial fibrillation. It entails renal excretion, and dose adjustments are necessary for patients with renal impairment. It is contraindicated in patients with severe renal disease (creatinine clearance < 30 mL/min). Doses for DVT prophylaxis are 150 or 220 mg. For atrial fibrillation, it is given as 150 mg twice daily. The anticoagulant effect of dabigatran cannot be reliably assessed with the PT or PTT. A modified thrombin time or an ecarin coagulation assay may be useful in monitoring this medication; however, the correlation of these tests with risk of hemorrhage has not been validated.

There is no specific antidote for the reversal of any of the DTIs. Management of bleeding remains supportive, and although hemodialysis can remove some of the drug from the bloodstream, the efficacy of this treatment for clinical bleeding has not been shown. The reversal of anticoagulant effect of dabigatran and rivaroxaban with PCCs has been studied in human volunteers. Although parameters of coagulation (including the INR, PTT, thrombin time, and endogenous thrombin potential) could be normalized in patient’s receiving rivaroxaban, no effect was seen in patients receiving dabigatran.

In a human study, desmopressin was given to 10 healthy volunteers. Samples showed an increase in factor VIII; C levels and a decrease in the hirudin induced prolongation of aPTT. This was not noted at higher doses of hirudin. In another study in which blood samples were analyzed ex vivo, rFVIIa improved bleeding parameters in argatroban- and bivalirudin-containing blood samples. There are case reports of the successful use of a variety of options, including FFP for argatroban overdose, and hemodialysis with modified ultrafiltration in conjunction with FFP, cryoprecipitate, and rFVIIa in a patient with persistent hemorrhage after cardiopulmonary bypass. Thus, desmopressin, rFVIIa, or clotting factors can be considered, but there are no clinical studies demonstrating clinical efficacy.

These observations suggest that none of the currently available approaches to anticoagulant reversal will be useful in patients who have bleeding events when taking dabigatran. Careful consideration should be given to its use in patients (particularly the elderly) who might have impaired renal clearance of the medication or who are at a high risk for falls and head trauma.

**Antiplatelet Agents**

**Aspirin**

Aspirin is one of the most commonly used medications. It has anti-inflammatory, antipyretic, and antiplatelet activities. It exerts its antiplatelet effect by irreversibly inactivating cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). These enzymes catalyze the first step in prostaglandin synthesis. COX-1 is responsible for the synthesis of thromboxane, an important prostaglandin for platelet aggregation. The half-life of aspirin is 15 to 20 minutes, but platelets do not have the ability to
synthesize new enzyme, so platelets are inhibited for the duration of their life span. The effect of aspirin dissipates 5 to 7 days after the last dose as the inactivated platelets are removed and replaced by cells with intact thromboxane synthesis. The acute reversal of the antiplatelet effect of aspirin requires platelet transfusion.

Another approach to the reversal of aspirin-mediated platelet dysfunction is to administer desmopressin. Desmopressin, also known as 1-deamino-8-D-arginine vasopressin (DDAVP), is used in the management of patients with hemophilia A and von Willebrand disease.\textsuperscript{48} It does not increase platelet number or enhance platelet aggregation, but it does enhance platelet adhesion to the vessel wall, possibly by its ability to increase the concentrations of factor VIII and von Willebrand factor. It is used routinely in uremic patients to improve platelet function. Its use has been suggested in patients treated with aspirin. In a randomized double-blind study, aspirin or placebo was administered to healthy volunteers.\textsuperscript{49} DDAVP was given as one or two intravenous doses. DDAVP increased platelet adhesiveness in both groups, and it normalized in the group treated with aspirin. Also noted was shortening of the bleeding time in the aspirin-treated group. This effect lasted about 3 hours and was extended with the second dose of DDAVP. A dose of 0.3 µg/kg is routinely given. Of note, there are no studies evaluating its effect on aspirin-medicated platelet dysfunction and bleeding in a clinical setting.

**Thienopyridines**

Clopidogrel is the most widely used drug in this category. It inhibits adenosine diphosphate (ADP)-mediated platelet activation by irreversibly binding to the P2Y12 receptor.\textsuperscript{50} It has a half-life of 8 hours. As with aspirin, the effect of clopidogrel persists after the clearance of the drug, and dissipation of its anticoagulant effect depends on the production of platelets with functioning P2Y12 receptors. Consequently, immediate reversal of the clopidogrel effect would require platelet transfusion. In a retrospective study of patients with ICH, the impact of platelet transfusion was examined.\textsuperscript{51} More patients taking clopidogrel with or without aspirin experienced hematoma enlargement. Platelet transfusion had no impact, but the number of patients in this category was small. There was also an increased trend toward in-hospital mortality. Desmopressin also has been evaluated as an agent to reverse the antiplatelet effect of clopidogrel. Healthy volunteers were given clopidogrel and then randomized to receive nasal desmopressin or placebo.\textsuperscript{52} Platelet reactivity and function was improved. Once again, there are no studies evaluating desmopressin in the setting of bleeding.

Prasugrel is another thienopyridine that is used in the management of coronary artery disease. It has a mechanism similar to that of clopidogrel and a shorter half-life of 3.7 hours.\textsuperscript{53} Its safety and efficacy were compared with those of clopidogrel in a phase 3 trial. There was an increase in fatal bleeding with prasugrel. The incidence of ICH was rare but similar.\textsuperscript{54} There are no data on reversal strategies, but one may hypothesize that they would be similar to those of clopidogrel.

**Conclusion**

Anticoagulant drugs have complex pharmacokinetics and narrow therapeutic indices. Patients who require anticoagulation are often medically complex and are subject to complications should they require either elective or emergent neurosurg-
gery. It is essential that the risks and benefit of interruption, reversal, or initiation of anticoagulation be coordinated between the treating surgeons and physicians to enhance the safe care of the patient in this high-risk area of medicine.

**KEY POINTS**

- The reversal of anticoagulation by VKAs is a two-step process. Immediate reversal is achieved by replacement of coagulation factors with plasma or coagulation factor concentrates; long-term correction of the anticoagulant effect requires vitamin K.
- Prothrombin complex concentrates are more beneficial in the rapid correction of the effect of VKAs than is plasma.
- Recombinant factor VIIa has not been shown to improve outcomes in patients with intracerebral hemorrhage.
- The anticoagulant effects of anti-Xa inhibitors (rivaroxaban, low molecular weight heparin, and fondaparinux) may be partially reversed with recombinant VIIa or PCCs.
- The anticoagulant effect of direct thrombin inhibitors is very difficult to reverse.
- Immediate reversal of the effects of aspirin, clopidogrel, and prasugrel requires platelet transfusions.

**REVIEW QUESTIONS**

1. The vitamin K antagonist anticoagulants include:
   A. Unfractionated heparin  
   B. LMWH  
   C. Warfarin  
   D. Clopidogrel  
   E. Dabigatran

2. The reversal of common oral anticoagulants typically involves administering:
   A. Vitamin K  
   B. Fresh frozen plasma  
   C. Protamine  
   D. rFVIIa  
   E. Vasopressin

3. True or false:
   A. The half-life of unfractionated heparin (UFH) is 60 to 90 minutes.  
   B. LMWHs are monitored with the PTT.  
   C. The half-life of LMWHs is 17 to 21 hours.  
   D. Protamine sulfate is effective for reversal of both UFH and LMWHs.  
   E. Fondaparinux is reversed with protamine sulfate.
II Hemostasis and Coagulation

4. True or false:
   A. The half-life of aspirin is 6 hours.
   B. Aspirin activates COX-1 and COX-2.
   C. The effects of aspirin on platelet function are permanent.
   D. The mean life span of platelets is 7 to 10 days.
   E. DDAVP administered IV may improve platelet adhesion to vessel walls for up to 3 hours after a single dose.

5. True or false:
   A. Clopidogrel inhibits ADP-mediated platelet activation by transiently binding to the P2Y12 receptor on the platelet membrane.
   B. Clopidogrel has a half-life of 8 hours.
   C. Clopidogrel has a minor effect on platelet function and can be continued prior to and during most neurosurgical procedures.
   D. Immediate reversal of clopidogrel requires a platelet transfusion.
   E. DDAVP administered IV may improve platelet adhesion to vessel walls for up to 3 hours after a single dose.

References

37. Rupprecht HJ, Blank R. Clinical pharmacology of direct and indirect factor Xa inhibitors. Drugs 2010;70:2153–2170 PubMed

ANSWER KEY

1. C
2. A, B
3. A: True; B: False; C: True; D: True; E: False
4. A: False; B: False; C: True; D: True; E: False
5. A: False; B: True; C: False; D: True; E: True
Herbal Products and Supplements Affecting Coagulation
Omar Tanweer, Shaun David Rodgers, and John G. Golfinos

A neurosurgical procedure may be meticulously planned for hemostasis preoperatively, intraoperatively, and postoperatively. But some outside influences may prove bothersome or outright dangerous to patients. Some of these influences occur in the form of extraneous substances, such as fish oil, herbal supplements, and vitamin E. Table 6.1 summarizes the supplements that are discussed in this chapter. The increased use of herbal supplements warrants consideration in all patients. Neurosurgeons must be familiar with the potential perioperative effects of such substances. A recent evaluation of perioperative neurosurgical patients focused on platelet count, partial thromboplastin time (PTT), and prothrombin time/international normalized ratio (PT/INR). We advocate strict screening of herbal and dietary supplements because of their potential to alter hemostasis in the neurosurgical patient and because of the serious possible consequences of even small amounts of bleeding in the confined space of the skull.

Fish Oil

Fish oil may pose the most substantial risk to the neurosurgery patient, given its widespread use in the general population. Fish oil (omega-3 fatty acids) is taken by the patient, or prescribed by a physician, to reduce triglycerides and hyperlipidemia. The recommended dose for fish oil is 1 to 4 g per day. Research has suggested that fish oil may affect platelet composition and alter platelet function. Bleeding time has been elevated in healthy volunteers. The mechanism appears to be related to adenosine diphosphate (ADP) blockade and thromboxane. Some authors have downplayed fish oil’s effect on platelets. A recent article with an extremely small sample size suggested that fish oil was safe in spine surgery. But this conclusion seems unwarranted at this early juncture. Of particular concern would be cranial surgery because there are no studies to support the use, or the cessation of use, of fish oil. The theoretical and anecdotal risk remains high. In our practice, until further evidence becomes available, we have chosen to delay elective surgery for 2 weeks in patients who were taking fish oils to allow the effects to dissipate. Fig. 6.1 provides a simplified mechanistic diagram of the interplay between coagulation factors and supplements.

Garlic

Garlic (Allium sativum) is of the onion family and has gained commercial popularity among herbal treatments over the last decade. In 2009, it was the fourth biggest
Table 6.1  Supplements and Their Uses

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Proposed Conditions Treated</th>
<th>Usual Dosing/Day</th>
<th>Mechanism for Increased Bleeding</th>
<th>Suggested Perioperative Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish oil (eicosapentaenoic acid)</td>
<td>Hyperlipidemia, hypertriglyceridemia</td>
<td>1–4 g per day</td>
<td>Inhibit cyclooxygenase, decrease thromboxane; inhibit ADP</td>
<td>Withhold for 14 days preoperatively</td>
</tr>
<tr>
<td>Garlic (Allium sativum)</td>
<td>Hyperlipidemia, hypertension, infection</td>
<td>1–2 cloves: 4 g Extract: 300 mg</td>
<td>Antiplatelet via thromboxane and ADP</td>
<td>Withhold 7 days preoperatively</td>
</tr>
<tr>
<td>Ginkgo (Ginkgo biloba)</td>
<td>Alzheimer’s dementia, cognitive enhancement, erectile dysfunction, peripheral vascular disease (PVD)</td>
<td>Extract: 80 mg</td>
<td>Antiplatelet via decreased PAF</td>
<td>Withhold 36 hours before surgery; half-life of 10 hours</td>
</tr>
<tr>
<td>Ginseng (Panax ginseng)</td>
<td>Alertness</td>
<td>Extract: 100 mg</td>
<td>Antiplatelet via decreased PAF and thromboxane</td>
<td>Withhold for 7 days; potential irreversible effects on platelets</td>
</tr>
<tr>
<td>Ginger (Zingiber officinale)</td>
<td>Nausea, gastrointestinal disturbances</td>
<td>4 g</td>
<td>Antiplatelet via decreased thromboxane</td>
<td>No supporting evidence for when to withhold preoperatively</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Antioxidant</td>
<td>100 mg (22.4 IU)</td>
<td>Reduces aggregation of platelets by reducing efficacy of thrombin</td>
<td>Withhold for 2–3 weeks prior to surgery</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADP, adenosine diphosphate; PAF, platelet-aggregating factor.

**Note:** Bleeding risks increase as intake surpasses the recommended daily dosing, which can be assessed by careful medicinal reconciliation.
selling herbal supplement, with sales of more than $17 million in the United States. The purported benefits include lowering blood pressure and cholesterol, and prevention of infections and of myocardial infarction. The underlying mechanism of the proposed benefits involves its antiplatelet activity. In vitro and in vivo studies have shown the antiplatelet activity to be mediated through blockade of the ADP receptor, thromboxane reduction, and reduction of calcium mobilization.

Evidence of increased bleeding risk in patients who take garlic has been noted in multiple case reports of spinal epidural hematomata and postoperative bleeding. In addition, studies have shown that there is a significant interaction with warfarin and aspirin, resulting in increased and unpredictable drug effects on anticoagulation. Although these data do not come from randomized controlled trials, there has been a general consensus to recommend withholding garlic 7 days preoperatively.

**Ginkgo**

Ginkgo (*Ginkgo biloba*) is an herbal preparation from the ginkgo tree, also known as the maidenhair tree. The use of this herbal remedy can be traced centuries back in Chinese history, and over the last decade it has become one of the top selling herbal supplements in the United States. Ginkgo can be taken in tablets, capsules, sublingual sprays, nutrition bars, and energy drinks. The proposed benefits include prevention of onset of Alzheimer’s dementia, increased attentiveness and
information processing, and treatment of erectile dysfunction and peripheral intermittent claudication. The principle behind the proposed benefits of increased cognition is thought to be increased blood flow, through direct antiplatelet effects and through increased oxygen extraction by brain tissue. In vitro studies have shown that antiplatelet activity may be mediated by reduction of the effect of platelet-activating factor (PAF).

Increased predisposition to bleeding has been reported in case reports, including spontaneous intraparenchymal hemorrhage, subarachnoid hemorrhage, and subdural hematoma. However the majority of case reports mention concomitant use of aspirin or warfarin. Although studies have found no hemorrhage in cohorts of healthy volunteers, the general consensus from the reported instances of hemorrhage is to withhold ginkgo preoperatively. Due to a half-life of only 10 hours, the recommendation is to withhold it for at least 36 hours before surgical intervention.

**Ginseng**

Ginseng (*Panax ginseng*) is a perennial plant found in China, Korea, and Vietnam. Extracts have been used as a stimulant and can be found in tablet form even in energy drinks. Scattered case reports of ginseng's causing bleeding have prompted in vitro studies demonstrating antiplatelet activity by inhibition of thromboxane production and PAF. Excessive bleeding has not been reported when intake is limited to daily dosage recommendations. But due to potential irreversible effects on platelets, the current recommendation is to withhold ginseng 7 days preoperatively.

**Ginger**

Ginger is a tuber of the *Zingiber officinale* plant. It is used as a remedy for nausea, dyspepsia, and gastrointestinal disturbances. Historically, ginger can be traced to cultivation in China thousands of years ago. There are no reports in the literature of clinically relevant hemorrhage attributed solely to ginger intake. However, in vitro and animal studies have shown antiplatelet activity by modulation of the aggregation pathway through thromboxane inhibition. There is no supporting evidence to guide perioperative management; however, if a patient has used ginger supplementation for a prolonged time at above the daily recommended dose of 4 g, consideration should be given to recommending preoperative cessation.

**Vitamin E**

Vitamin E has gained popularity for its antioxidant properties. The recommended daily dietary allowance is 15 mg, but commercially available supplements are frequently 10 to 20 times that amount. Reports of anticoagulation properties and even incidents of subarachnoid hemorrhage have been noted with doses as low as 50 mg per day, but this finding has been inconsistent at best. In a study of healthy volunteers, increased bleeding risks were shown to be mediated through an effect on thrombin-mediated platelet aggregation. No strong supporting evidence exists for perioperative management of vitamin E use, but some surgical practices recommend 2 to 3 weeks of cessation prior to surgery.
KEY POINTS

- Herbal supplements may influence the coagulation status of a patient, and their use must be screened for preoperatively.
- The administration of fish oil may elevate bleeding time.
- Garlic, ginseng, ginger, and ginkgo have antiplatelet properties.
- Vitamin E may influence thrombin-mediated platelet aggregation.

REVIEW QUESTIONS

1. The impact of the use of fish oil (omega-3 fatty acids) on bleeding in cranial surgery is:
   A. Extremely risky
   B. Negative
   C. Negligible
   D. Unknown, with no significant studies shedding light on the matter at this time

2. If a patient is taking garlic routinely, the recommendation should be:
   A. Infuse protamine
   B. Proceed with surgery the next day without risk
   C. Wait 24 hours prior to surgery
   D. Withhold garlic and wait 7 days prior to surgery

3. Ginseng has been reported to demonstrate significant antiplatelet activity by inhibiting platelet-activating factor. The current recommendation prior to surgery is:
   A. Discontinue the day prior to surgery
   B. Do not discontinue the supplement
   C. Discontinue the supplement 7 days prior to surgery
   D. Infuse platelets prior to elective surgery

4. If a patient routinely takes ginger, the recommendation should be:
   A. Cessation prior to surgery, even though there is no supporting evidence to guide management
   B. Continue ginger supplement in the perioperative period
   C. Infuse platelets prior to elective surgery
   D. No cessation prior to surgery, as there is no theoretical risk

References


ANSWER KEY

1. D
2. D
3. C
4. A
III

Blood Loss and Replacement
Blood loss, a universal concern in surgery, is only somewhat mitigated by the possibility of blood replacement by transfusion. It is better to avoid blood loss than to control or replete it. Ideally, careful surgery includes strategies and techniques to reduce blood loss, to maintain normal coagulation status, and to actively recover blood where possible. Adherence to these practices minimizes blood loss and therefore reduces its negative hemodynamic consequences and the need for transfusions.

The volume of blood loss associated with a surgery highly depends on the type of surgery performed. Some neurosurgical procedures, such as clipping of a ruptured aneurysm, usually entail very little blood loss, but occasionally blood loss can be extreme. Excessive surgical bleeding causes hypovolemia, hypotension, hemodynamic instability, and anemia, and reduces oxygen delivery to tissues, with a subsequent increase in postoperative rates of morbidity and mortality.¹

Steps to anticipate and reduce blood loss should be a consideration in every neurosurgical case. Allogeneic blood transfusion is associated with adverse effects, including the potential for transmission of infectious diseases, immunosuppression, transfusion-related acute lung injury, transfusion-related allergic reactions, and graft versus host reactions. The fiscal implications of blood transfusions are significant in terms of both the direct cost of a transfusion as well as costs related to additional treatments for side effects and prolonged hospitalization.

History

At the end of the 19th century, the early evolution of the specialty of neurologic surgery was restricted by complications related to infection, increased intracranial pressure, and excessive intraoperative blood loss. These complications often resulted in mortality rates of 30 to 50%. An improved understanding of pathophysiological factors involved in increased intracranial pressure, along with meticulous surgical techniques learned from William Halsted, allowed Harvey Cushing to increase the safety of neurosurgical procedures that were then in their infancy. Cushing’s later development of the “silver clip” and incorporation of electrosurgical cautery techniques facilitated safe resection of brain tumors previously assumed to be inoperable. The inability to control bleeding from vascular lesions such as arteriovenous malformations, aneurysms, and certain brain tumors made these the last lesions to become operated on routinely. Better understanding of anatomy and fundamental measures to control blood loss, such as proximal vascular control, the use of temporary clips, bipolar electrocautery, and endovascular embolization, improved surgical outcomes. These pivotal accomplishments paved the way for the present evolution of our specialty.²
Blood Volume and Constituents

Blood makes up about 8% of human body weight and has about the same density as water. The average 70-kg male has a blood volume of about 5 L. The erythrocytic (red blood cell) component, which constitutes the hematocrit, is 40% of the blood volume in women and 45% in men. Blood components include erythrocytes, leukocytes, platelets, and plasma. All of these components are consumed or lost in the presence of bleeding, and all are important for maintaining normal health and physiologic function.

Factors Affecting Blood Loss

Blood can be lost from arteries, capillaries, and veins. Some trauma to these structures is inevitable during the course of surgery. Nonetheless, any surgical strategy should include the goal of minimizing blood loss. A surgical route that does not violate major vascular structures and that exposes them in a controlled fashion is preferred. Anticipation of arteries during dissection, including their rapid identification and preservation or control, is a basic step. For both arteries and veins, preservation is usually preferred to sacrifice.

Artificial bleeding must be controlled by electrocoagulation or ligation but should rarely be relied on to stop spontaneously. Very small arterioles may stop bleeding spontaneously, but this form of hemostasis should be regarded with healthy suspicion. When possible, the avoidance of intraoperative or early postoperative hypotension may assist such passive hemostasis. Controlled hypotension must be balanced against the essential priority that brain and spinal cord perfusion must be adequate. Capillary bleeding stops spontaneously in the presence of adequate circulating and tissue coagulation factors.

Venous bleeding can often only be controlled with tamponade, frequently with preservation of the vein. Simple maneuvers such as elevation of the surgical site also may aid venous hemostasis. If, however, the site is elevated too much, so that the local venous pressure becomes negative, there is the risk of air embolism. This risk is particularly problematic in regions with noncollapsing veins (e.g., the major cranial venous sinuses).3

When possible, a patient should enter surgery with as near normal coagulation status as possible. As surgery progresses, maintenance of normocoagulation requires vigilance and anticipation. Preservation of normocoagulation is aided by normothermia during surgery, because of the deleterious effects of hypothermia on platelet function.4 Blood coagulability can also be compromised by fluid replacement as a result of hemodilution. Moderate crystalloid substitution accelerates rather than inhibits blood coagulation; however, with advanced crystalloid replacement, profound hemodilution may cause blood coagulation to become compromised.5 The use of colloids also may compromise coagulation; this effect is seen with hydroxyethyl starch more than with gelatin and serum albumin.6

The substrates of blood clotting must be sufficient to drive the clotting process. The patient’s baseline level of coagulation factors may be affected by a variety of physiological and pathological factors or conditions such as liver disease, autoimmune diseases, or von Willebrand disease, among many others. During surgery, consumption of clotting factors can lead to coagulopathy when a large volume of blood is lost or a large surface is traumatized. Disseminated intravascular coagulation can also consume necessary factors. Finally, extensive brain tissue trauma
(e.g., with gunshot wounds to the head) can release tissue thromboplastins, resulting in ineffective coagulation.

Surgical control of bleeding usually involves gross closure of bleeding vessels with electrocautery, clips, or ligatures. Electrocautery coagulates proteins in blood vessel walls and surrounding tissues, occluding the lumen. This kind of closure is fairly reliable as long as generous closure of the vessel is achieved. As a rule, arteries require more coagulation than veins. Tumor vessels or arteriovenous malformation vessels sometimes require more coagulation with cautery than normal vessels. Larger vessels (greater than 1–2 mm in diameter) are often best closed with a clip. Temporary and permanent aneurysm and arteriovenous malformation clips that are rated to closing pressures that exceed even the highest possible supranormal physiological pressures are commercially available. Titanium or other alloys that are compatible with magnetic resonance imaging (MRI) should be used when possible. Proximal control of bleeding with clips must proceed with caution, because the need to control blood loss must be balanced against the risk of ischemia in the distal territory of the involved vessel.

The following sections discuss the physiology of hemostasis, pharmacological and topical hemostatic agents for controlling blood loss, the emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients, and control of blood loss in specific neurosurgical situations.

**Physiological Impact of Blood Loss**

In response to blood loss, the body compensates physiologically to maintain blood pressure and perfusion of key organs. At first, tachycardia occurs to increase cardiac output. Concomitantly, vasoconstriction occurs peripherally, supporting the blood pressure by decreasing flow to the skin and muscle. Vasoconstriction proceeds to shift flow away from other nonessential organs, such as the gastrointestinal tract and kidneys, while maintaining flow to the brain, heart, and lungs. As acidosis and hypercarbia occur, a shift occurs in the hemoglobin-binding curve to promote release of oxygen. The impact of blood loss is a function of both the volume and rate of blood loss. There is no good formal classification of neurosurgical blood loss or even of surgical blood loss in general. Blood loss related to hemorrhage, such as that sustained in trauma, is divided into four classes by the American College of Surgeons in its Advanced Trauma Life Support (ATLS) courses. Although surgical bleeding may follow a slightly different course because it is actively managed and occurs under anesthesia, the general classification is useful. A class I hemorrhage constitutes blood loss of 15% or less of circulating blood volume. Hemodynamic changes in the vital signs are seldom related to physiological compensation such as mild vasoconstriction, which is often not clinically apparent.

Class II hemorrhage involves loss of 15 to 30% of blood volume. Tachycardia is necessary to compensate for the loss of volume by increasing cardiac output. The pulse pressure may narrow, and clinically apparent vasoconstriction, such as cooling of the extremities and blanching of the skin, may occur. Fluid resuscitation with crystalloids may be adequate to reverse this response.

Class III hemorrhage is defined as a loss of 30 to 40% of circulating blood volume. With this degree of blood loss, tachycardia increases, the blood pressure falls, and more intense peripheral vasoconstriction occurs. Compensation occurs in the periphery and in some solid organs that would be unsustainable if the blood loss
Blood Loss and Replacement

is not eventually reversed. Fluid resuscitation with volume expanders will be necessary. If available, blood transfusion is considered at this point.

Class IV hemorrhage is defined as a loss of 40% or more of circulating blood volume. Physiological mechanisms cannot compensate for the blood loss. If aggressive resuscitation with volume replacement, volume expanders, or blood is not instituted, death occurs. Healthy patients may be able to compensate more fully for blood loss because of a better ability to increase heart rate, stroke volume, or vascular tone. Older or less healthy patients may suffer the ill effects at lower degrees of blood loss, or they may suffer permanent damage at an earlier stage despite a lesser degree of blood loss.

These numbers also can serve as a rough guide during surgery. Typically, blood loss on the order of 15% or less is well tolerated during surgery, and no replacement other than crystalloid or colloidal fluids is necessary. As blood loss increases, resuscitation should be ongoing and should escalate through colloids to blood products. Careful anesthesia monitoring for signs of cardiovascular instability, hypotension, and possibly cardiovascular collapse is essential. If only colloids are used, the hematocrit and hemoglobin concentration begins to fall through hemodilution. However, there is no strict hematocrit percentage that is considered critical for blood replacement. This level depends on several patient factors.

**Physiology of Hemostasis**

For blood loss to be minimized during neurosurgical procedures, the patient should have a functioning hemostatic system. Hemostasis depends on a successful balance among the coagulation, complement, and fibrinolytic pathways. Complex interactions are necessary between plasma proteins, platelets, blood flow and viscosity, and the endothelium. Spontaneous clotting involves formation of the primary hemostatic plug at the site of a damaged vessel wall, which is the first event in the control of bleeding. In this mechanism, the glycoprotein (GP)Ib receptor on platelet membranes binds to von Willebrand factor (vWF), which is linked to the exposed subendothelium. This process enables platelets to adhere to the site of injury.

Adherent platelets become activated and undergo a conformational change, increasing their surface area contact with the subendothelium. Activated platelets also release adenosine diphosphate (ADP) and thromboxane A₂, which, in concert with thrombin derived from the coagulation cascade, stimulate platelet aggregation via receptor-mediated metabolic processes. ADP, thromboxane A₂, and thrombin bind their respective platelet membrane receptors, thereby activating the platelet surface receptor GPIIb/IIIa to bind soluble extracellular ligands such as plasma fibrinogen and vWF. These ligands link to GPIIb/IIIa receptors on adjacent platelet membranes, enhancing the initial adhesion and allowing other platelets to accrete on those already attached, thus forming a platelet plug at the site of injury.

**Coagulation Cascade**

Coagulation involves the laying down of a strong fibrin mesh through the primary platelet plug and is brought about by the action of a sequence of proenzymes and cofactors that work in concert to generate the final enzyme, thrombin. Thrombin then directly cleaves fibrinogen to produce fibrin. The enzymes involved in blood
Principles of Blood Loss

Coagulation belong to the serine protease family. This class of enzymes has a common mechanism of action that requires the catalytic triad of serine, aspartic acid, and histidine within the active site. Activation of the coagulation cascade triggers several physiological pathways that tend to counteract and limit the spread of coagulation to the area of injury. This balance is necessary to allow targeted clotting that prevents further blood loss but does not interfere with flow in normal vessels.

Emergency Reversal of Anticoagulation and Antiplatelet Therapies

As patients are increasingly treated with anticoagulants and antiplatelet agents, it is essential that physicians who care for them understand the pathways these drugs act on and the degree to which they can affect perioperative blood loss, and that they recognize how these drugs can be manipulated to restore hemostasis (Table 7.1). Not only does the risk and incidence (7- to 10-fold greater) of intracranial hemorrhage increase in patients on anticoagulants compared with those who are not, but anticoagulant-induced hematomas tend to be larger and more likely to expand.

Clopidogrel (trade name Plavix) and ticlopidine (Ticlid) are drugs that inhibit the P2Y12 ADP receptor of platelet membranes, preventing activation of the GPIIb/IIIa pathway and thus platelet aggregation and clot formation. Because there is a finite amount of circulating metabolite available to inactivate existing platelets, the anticoagulant effect of these drugs can be corrected with platelet administration.

Another frequently used anticoagulant, Coumadin, acts by depleting vitamin K–dependent coagulation factors (factors II, VII, IX, and X, protein C, and protein S). Correction of the international normalized ratio (see Chapter 9) involves replacement of vitamin K and the dependent coagulation factors. A few options are available for replacing coagulation factors: fresh frozen plasma, prothrombin complex concentrate (PCC), and factor VIIa. PCC is available in a three- or four-factor form. The four-factor form includes factors II, VII, IX, and X, whereas the three-factor form includes factors II, IX, and X only and must be supplemented with additional factor VII. Because transfused factors have a limited half-life, vitamin K must always be administered for further hepatic production and replacement of factors.

Dabigatran etexilate is the first oral direct thrombin inhibitor available for anticoagulation. It presents a challenge, because the typical reversal agents (fresh frozen plasma, PCC, and vitamin K) do not reverse its anticoagulant effects, and it is not easily monitored.

Pharmacological Hemostatic Agents

A limited number of pharmacological agents have been used to correct hemostatic defects in the perioperative period. The lack of clear understanding regarding the pathogenesis of perioperative bleeding as well as its multifactorial origins has limited the development of specific and new hemostatic agents. Although several good agents are available to assist surgeons with the intraoperative control of bleeding, highly specific agents for the control of neurosurgical bleeding do not exist.

One agent that has been used intraoperatively is desmopressin. Two studies have evaluated the use of desmopressin in patients undergoing spinal fusion sur-
### Table 7.1 Anticoagulants/Antiplatelet Agents and Their Emergency Reversal

<table>
<thead>
<tr>
<th>Anticoagulant/Antiplatelet Agent</th>
<th>Reversal</th>
<th>Laboratory Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K, 5–10 mg IV 3-factor PCC, 4000 IU Low dose rFVIIa, 1.0 mg</td>
<td>PT/INR</td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Stop infusion Protamine sulfate, 1 mg for each 100 U of active heparin</td>
<td>PTT</td>
<td>FFP contraindicated; slow administration (&lt; 5 mg/min) to avoid protamine-induced bronchoconstriction or hypotension</td>
</tr>
<tr>
<td>Low molecular weight heparin (LMWH)</td>
<td>Protamine sulfate 1 mg for each 1 mg of LMWH; consider activated PCC (FEIBA); consider rFVIIa</td>
<td>Anti-XA assay</td>
<td>Protamine can achieve only partial reversal</td>
</tr>
<tr>
<td>DTI</td>
<td>No specific antidote; DDAVP, 0.3 µg/kg; consider rFVIIa (with extreme caution in HIT)</td>
<td>PTT</td>
<td>Caution hyponatremia, seizures, and elevated ICP with DDAVP</td>
</tr>
<tr>
<td>Pentasaccharide</td>
<td>rFVIIa, 30–90 µg/kg</td>
<td>Anti-XA assay</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1 U platelet transfusion; consider DDAVP, 0.3 µg/kg; consider rFVIIa, 30–90 µg/kg</td>
<td>Consider PFA-100 testing</td>
<td>Caution hyponatremia, seizures, and elevated ICP with DDAVP</td>
</tr>
<tr>
<td>Clopidogrel or ticlopidine</td>
<td>2 U platelet transfusion; consider DDAVP 0.3 µg/kg; consider rFVIIa, 30–90 µg/kg; after 12 hours does not inactivate new platelets</td>
<td>Consider platelet aggregometry/clopidogrel inhibition panel</td>
<td>Caution hyponatremia, seizures, and elevated ICP with DDAVP</td>
</tr>
</tbody>
</table>

**Abbreviations:** DDAVP; 1-deamino-8-D-arginine vasopressin; DTI, direct thrombin inhibitors; FEIBA, facto eight inhibitor bypassing activity; FFP, fresh frozen plasma; HIT, heparin-induced thrombocytopenia; ICP, intracranial pressure; INR, international normalized ratio; PCC, prothrombin complex concentrate; PFA, Platelet Function Analyzer; PT, prothrombin time; PTT, partial thromboplastin time; rFVIIa, recombinant factor VIIa.

Drugs like epsilon-aminocaproic acid (EACA), tranexamic acid, nafamostat, aprotinin, and factor VIIa still await clinical trials before definitive conclusions can be made about their safety and exact role in the care of neurosurgical patients. A balance between desired and inappropriate reduction of fibrinolysis must be maintained. For instance, the use of EACA to prevent rebleeding in ruptured aneurysm care resulted in an unfavorably large increase in the complication of vasospasm. However, Starke and colleagues compared the short-term use of EACA (4 g intravenous loading dose, then 1 g/h for a maximum of 72 hours after onset of subarachnoid hemorrhage) to historical controls and demonstrated a decreased incidence of rebleeding and no significant increase in ischemic events. The relative safety and efficacy of a short course of EACA treatment for decreasing the risk of rebleeding have been supported by additional retrospective studies. However, prospective, controlled trials are still needed.

Tranexamic acid is another antifibrinolytic that has been found to reduce the risk of rebleeding without unacceptable complications of vasospasm or ischemic events when used in the short term. Aprotinin and nafamostat have been implicated in decreasing the risk of aneurysmal rebleeding. They also may help decrease cardiac perioperative blood loss and mortality, but they have not been well studied in the neurosurgical arena. Factor VIIa is Food and Drug Administration (FDA) approved for bleeding in patients with hemophilia A and B, and has been shown to rapidly correct Coumadin-related coagulopathies and to decrease hemorrhage expansion in patients with spontaneous hematoma. It is currently being studied as an agent to prevent aneurysmal rebleeding as well as to decrease the chances of intraoperative rupture of high-risk aneurysms.

Topical Hemostatic Agents

Achneck et al presented a comprehensive review of topical hemostatic agents, subcategorized as physical agents, absorbable agents, biologic agents, and synthetic agents. Such agents are widely used in both cranial and spinal neurosurgery. Each has application to one or more particular hemostatic challenges. For example, bone wax is well suited to covering noncollapsing channels, such as those that occur in cancellous bone or where emissary veins traverse bone. Foams are particularly effective for filling epidural spaces and tamponading compressible veins; woven cellulose forms a direct scaffold and barrier that may support blood coagulation to cover veins or venous sinuses without occluding them.

Surgical Techniques and Maneuvers to Minimize Blood Loss

A step-by-step analysis of a typical cranial surgery helps synthesize all considerations for minimizing blood loss. The surgeon is responsible for anticipating significant blood loss and for recognizing its occurrence during surgery. Pausing surgery with appropriate notification can allow the anesthesiologist and the rest of the team to “catch up” with current blood loss, to check for deficiencies in coagulation or clotting factors, or to prepare for additional blood loss. When surgical blood loss

7 Principles of Blood Loss
<table>
<thead>
<tr>
<th>Hemostatic Agent</th>
<th>Products</th>
<th>Mechanism of Action</th>
<th>Advantages/Recommended Use</th>
<th>Disadvantages/Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone wax</td>
<td>Bone wax</td>
<td>Tamponade through occlusion of bleeding channels in bone</td>
<td>Can effectively control bleeding from bone surfaces</td>
<td>Can impede bacterial clearance and act as a nidus for infection; therefore, use in a contaminated field; may embolize; should not be used where bone fusion is critical, as it is not absorbed by the body</td>
</tr>
<tr>
<td>Ostene</td>
<td>Alkylene oxide copolymers</td>
<td>Occlude bleeding channels in bone</td>
<td>Recommended for bleeding control on bone surfaces</td>
<td>Do not use at sites with active or latent infections</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Gelfoam, Gelfilm, Surgifoam</td>
<td>Provides physical matrix for clotting initiation</td>
<td>Effectively controls small vessel bleeding; may be used to control bleeding from bone; recommended as hemostatic plug wrapped in oxidized cellulose; absorbed by the body in 4–6 weeks; nonantigenic; neutral pH allows use with biological agents</td>
<td>Significant swelling in closed spaces may compress nerves; use around brisk arterial bleeding may dislodge sponge; may embolize in an intravascular compartment</td>
</tr>
<tr>
<td>Oxidized cellulose</td>
<td>Surgicel, Nu-Knit</td>
<td>Provides physical matrix for clotting initiation, low pH contributes to coagulative necrosis</td>
<td>Low pH antimicrobial effect; very good handling characteristics (best when applied dry); does not stick to instruments; dissolves in 2–6 weeks</td>
<td>Must not be used with other biological hemostatic agents (thrombin) because of low pH, which may increase inflammation of the surrounding tissue; caution when using near spinal cord as swelling and Surgicel fibers could pass through the intervertebral foramen causing cord compression</td>
</tr>
<tr>
<td>Hemostatic Agent Products</td>
<td>Mechanism of Action</td>
<td>Advantages/Recommended Use</td>
<td>Disadvantages/Caution Against Use</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Microfibrillar collagen</td>
<td>Platelet adherence and activation</td>
<td>No significant swelling; absorbed in &lt; 8 weeks; can control wide areas of parenchymal bleeding; effective despite profound heparinization because of its mechanism of action</td>
<td>Less effective in patients with thrombocytopenia; sticks to operator’s gloves; may bind to neural structures; caution with blood scavenging systems, as it can pass through filters</td>
<td></td>
</tr>
<tr>
<td>Thrombin</td>
<td>Converts fibrinogen to fibrin to form clots; activation of clotting factors</td>
<td>Effectively controls minor bleeding from capillaries and small venules when pressure or ligation is insufficient; easy application; fast acting</td>
<td>Bovine thrombin can cause immunologic response and possible increase in coagulopathy and thrombosis</td>
<td></td>
</tr>
<tr>
<td>Thrombin with gelatin FloSeal</td>
<td>Gelatin granules cross-linked into matrix and swell for tamponade effect, thrombin hemostatic effect</td>
<td>Better control of moderate arterial bleeding than fibrin sealants due to gelatin granule tamponade effect</td>
<td>Needs contact with blood as source of fibrinogen; can swell up to 20% in 10 minutes after application</td>
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is extreme, it may be reasonable to stage the surgery and finish when conditions are more favorable.

In the performance of a routine craniotomy, risk factors for abnormal coagulation status should be considered from the patient’s history and physical examination, including, but not limited to, a personal history or family history of prior abnormal bleeding or bruising; liver disease; exposure to anticoagulants or antiplatelet agents such as aspirin or other antiplatelet agents such as Coumadin, heparin, low molecular weight or fractionated heparin or other agents; and the presence of nutritional deficiencies, renal disease, and genetic antithrombotic or prothrombotic disease. Appropriate preoperative laboratory evaluation, including blood type and a screen or cross, should be undertaken.

The surgical plan should be designed to avoid unnecessary blood loss, should be understood by all team members, and should include an explicit discussion of expected blood loss. This step is now a part of the standard neurosurgical “time out” or “pause” practiced at many centers. The availability of blood replacement products or substitutes should be confirmed.

The patient’s position should allow the surgical site to be elevated if possible, and how to avoid venous compromise through kinking of veins in the neck should be considered. Immediate preoperative infiltration of the skin and scalp with a local anesthetic solution containing epinephrine may reduce blood loss. The scalp has a robust blood supply. Manual compression of the scalp during opening, application of clips to the incised scalp, and rapid coagulation with electrocautery of bleeding vessels can minimize bleeding. The scalp has a robust blood supply. Manual compression of the scalp during opening, application of clips to the incised scalp, and rapid coagulation with electrocautery of bleeding vessels can minimize bleeding. Bur holes and bone edges can be waxed. The scalp has a robust blood supply. Manual compression of the scalp during opening, application of clips to the incised scalp, and rapid coagulation with electrocautery of bleeding vessels can minimize bleeding.

Exerting care when the dura is dissected from underneath the bone flap before the kerf is cut with the craniotome can prevent injury to underlying veins or venous sinuses. The placement of snug dural tack-up sutures between the dura and bone may reduce epidural bleeding and certainly can be used to help control epidural bleeding. The dura should be incised so that underlying veins are not damaged. Intradural dissection should be performed in sharp and blunt fashion with meticulous respect for vascular structures. Where relevant, feeding or inflow vessels to the pathology should be controlled before the primary lesion is addressed.

When the surgeon is working over dural sinuses, the cut most likely to damage a vein should be performed first, so that a firm area of surrounding bone is available to tack up or to wax against. Cuts should be started near the sinus and then proceed away from the sinus to avoid catching the footplate of the craniotome under the dura and thereby damaging the veins. When damage occurs, elevation of the head may slow the blood flow, although air embolism may become a concern. A position neither promoting air intake nor promoting bleeding is ideal. Venous bleeding can almost always be stopped by simple tamponade. Large sinus defects can be closed by rolling a flap of the adjacent dura over the defect and suturing it in place. Intradurally, proximal control of blood vessels should be secured, where relevant. For some skull base pathologies, extracranial control of afferent vessels such as the cervical carotid in the neck is necessary to gain safe proximal control.

Meticulous hemostasis should be obtained at each level of closure. Postoperative maintenance of normocoagulability and normotension (or even mild hypotension where possible) may promote hemostasis. Maintenance of normothermia promotes effective coagulation.
Conclusion

Control of intraoperative blood loss requires contributions from both the surgeon and the anesthesiologist. Both should have a strong understanding of the physiological and hematological principles underlying blood loss. Planning appropriately, ruling out preoperative coagulation defects, anticipating significant blood loss, positioning the patient thoughtfully, controlling blood pressure, ensuring meticulous surgical hemostasis, maintaining normothermia, replacing fluids judiciously, and correcting clotting factor deficiencies are the basic components of obtaining hemostasis in the surgical field.

The use of anticoagulants and antiplatelet agents is increasing and likely will continue to do so. Intracranial hemorrhage associated with these agents must be reversed quickly to improve the likelihood of recovery. As new agents are used, neurosurgeons must be aware of the effective strategies available to reverse coagulopathy.

Further research on the role of pharmacological hemostatic agents is needed to define their role in preventing blood loss. Topical hemostatic agents have an established role in neurosurgery, and new agents continue to improve on older options.

KEY POINTS

• Blood loss is easier to avoid than to correct. Careful surgical planning and stepwise control of sources of bleeding can greatly reduce blood loss.
• Carefully monitoring blood loss in concert with the anesthesiologist allows fluid and blood to be replaced on a schedule that can prevent most of the negative sequelae of blood loss. Being too quick to dismiss the estimated blood loss as erroneous is done at one’s own peril.
• Occasionally, blood loss is best avoided by completing the surgical goal rapidly. For instance, some tumors are best removed quickly despite the ensuing blood loss, rather than slowly removing the lesion and continually trying to achieve hemostasis at an overall greater blood loss. When extreme blood loss is encountered, such as in spinal deformity operations, staging the procedure is a reasonable option.
• Blood volume makes up about 8% of human body weight.
• The average 70-kg male has a blood volume of about 5 L.
• The hematocrit is indicative of the red cell component of blood and is 40% for women and 45% for men.
• Preservation of normocoagulation is aided by normothermia.
• Hypothermia can adversely affect platelet function.
• Profound hemodilution with crystalloid or colloid solutions may compromise coagulation.
• Disseminated intravascular coagulation (DIC) may occur when a large volume of blood is lost or a large surface area is traumatized.
• Physiological impact of blood loss may include tachycardia; vasoconstriction; hypotension; and diminished blood supply to the brain, heart, and lungs, with clinical effects including cerebral and cardiac ischemia and renal failure.
• The severity of hemorrhage can be classified to aid in the implementation of management strategies.
• The principles of hemostasis include changes with the blood vessel, platelets, and the coagulation cascade.
Strategies exist to reverse the effects of antiplatelet agents and most agents that affect the coagulation cascade. Strategies for minimizing blood loss during surgery and for the use of topical hemostatic agents should be routinely employed.

### REVIEW QUESTIONS

1. Allogeneic blood transfusion uses:
   - Blood from the same individual
   - Blood from a crossmatched relative
   - Blood from a crossmatched nonrelative
   - Blood from a type O unmatched Rh compatible nonrelative
   - All of the above

2. Potential allogeneic blood transfusion reactions include:
   - Transmission of infectious diseases
   - Transfusion-related acute cardiomyopathy
   - Graft versus host reaction
   - Immunosuppression
   - Allergic reaction

3. Parameters suggesting severe blood loss include:
   - Blood loss between 10% and 15% of total blood volume
   - Bradycardia
   - Tachycardia
   - Vasodilation and hypotension
   - Diminished urine output and hypertension

4. Which of the following are steps involved in a functioning hemostatic system?
   - Formation of the primary hemostatic plug
   - Blood vessel dilation
   - Uncoupling of the GPIb receptor or platelet membranes from von Willebrand factor
   - Thrombin cleaving fibrinogen
   - Laying down a strong thrombin mesh

5. Which of the following statements about antiplatelet agents are true?
   - Clopidogrel inhibits the PGY_{12} ADP receptor on platelet membranes.
   - The platelet effect from aspirin is permanent.
   - The platelet effect from clopidogrel is temporary.
   - Platelet transfusion can reverse the effects of aspirin.
   - The average life span of a platelet is 3 days.

6. Which of the following agents are commonly used to assist with surgical hemostasis?
   - Bone wax
   - Bone cement
   - Oxidized gelatin
   - Microfibrillar collagen
   - Thrombin
References


<table>
<thead>
<tr>
<th>ANSWER KEY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. B, C, and D</td>
</tr>
<tr>
<td>2. A, C, D, and E</td>
</tr>
<tr>
<td>3. C</td>
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<tr>
<td>4. A and D</td>
</tr>
<tr>
<td>5. A, B, and D</td>
</tr>
<tr>
<td>6. A, D, and E</td>
</tr>
</tbody>
</table>
A thorough understanding of indications for blood replacement is essential for all neurosurgeons. The breadth of neurosurgical procedures, the often critically ill status of the neurosurgical patient population, and the unique perfusion requirements of the brain and spinal cord necessitate special consideration. This chapter discusses the assessment, rationale, indications, complications, and alternatives for blood replacement in neurosurgical patients.

Preoperative Assessment

Preoperative laboratory data can be helpful in assessing the need for or anticipating the likelihood of blood replacement. A preoperative analysis of hemoglobin and hematocrit levels can indicate the presence of anemia and establish a baseline for future transfusions. A patient with chronic anemia may better tolerate a lower hemoglobin level than a patient experiencing acute blood loss. The finding of unexpected anemia should prompt a determination of the underlying cause before surgery. The platelet count, prothrombin time (PT), and partial thromboplastin time (PTT) provide an evaluation of the substrates for blood clotting. Abnormalities should be investigated and corrected when possible. Finally, deficiencies in any of the above factors or anticipation of significant blood loss can help the surgeon prepare by securing blood products for transfusion (especially the option of autologous donation), requesting blood recovery devices, or modifying the surgical strategy.

Laboratory Evaluation of Coagulation

Given the potentially devastating consequences of bleeding complications in neurosurgical patients, a thorough preoperative assessment of bleeding risk is critical. The most important aspect of the assessment is a detailed bleeding history. The patient should be questioned regarding a bleeding tendency, easy bruising, bleeding problems associated with previous surgeries, and a family history of bleeding pathologies. A patient who is a reliable historian and has no history of bleeding problems is at very low risk for bleeding complications from intrinsic hypocoagulability. Laboratory assessment includes evaluation of the clotting cascade and the effectiveness of platelet function as detailed below. In a neurosurgical context they are useful before, during, and after surgery.
Prothrombin Time and the International Normalized Ratio

The PT evaluates the effectiveness of the extrinsic pathway of coagulation, specifically the tissue factor (TF) and final common pathways. The PT is used to monitor the clotting potential of blood with warfarin therapy, vitamin K deficiency, and the adequacy of liver synthesis of clotting factors. To perform the test, a suspension of tissue thromboplastin (TF + phospholipids) and calcium chloride is added to platelet-poor plasma. The time to the formation of a fibrin clot is the PT.

Because different sensitivities of tissue thromboplastin reagents produce variability in PT, the international normalized ratio (INR) was introduced. It is calculated using the following formula: (Patient PT/Mean normal PT)^ISI, where ISI is the International Sensitivity Index, a value assigned to the PT reagent when compared with a World Health Organization reference standard. The INR was standardized using plasma from patients on chronic warfarin therapy, which affects only vitamin K–dependent factors (VKDFs) II, VII, IX, and X. The INR will not necessarily be abnormal if other clotting factors are affected.

Partial Thromboplastin Time

The PTT (or activated PTT) test evaluates the intrinsic pathway, including contact factors (factor XII, high molecular weight kininogen, and prekallikrein) and factors VIII, IX, and XI. Specifically, it evaluates the coagulation of plasma induced by the activation of factor XII with a surface-activating agent. Silica or kaolin is used in the presence of a phospholipid extract of brain lacking tissue factor, which is therefore a partial thromboplastin. PTT is useful for monitoring the effects of heparin therapy and the direct thrombin inhibitors.

Platelet Count

The laboratory evaluation of blood components should include a platelet count. The normal range is usually defined as 150 to 400 × 10^9/L; however, a normal platelet count does not guarantee normal platelet function. Some authorities think that minor brain surgery can be performed safely with platelet counts between 60 and 100 × 10^9/L. Counts between 20 and 60 × 10^9/L may be associated with excessive bleeding that does not cease with the usual maneuvers or in a timely fashion during surgery. Spontaneous bleeding seldom occurs until platelet counts are less than 20 × 10^9/L.

The cause of thrombocytopenia is important when considering its probable impact on bleeding. The differential diagnosis includes massive transfusion, hemodialysis, platelet sequestration (e.g., from hypersplenism), decreased production from congenital or acquired anemias (e.g., from aplastic anemia, Wiskott-Aldrich syndrome, ionizing radiation, myelosuppressive drug use, nutritional deficiencies), immune destruction (e.g., from idiopathic thrombocytopenic purpura) or nonimmune destruction (e.g., von Willebrand disease, sepsis, thrombotic thrombocytopenic purpura, burns), or heparin exposure. When the result is unexpected, the test should be repeated to rule out pseudothrombocytopenia or artifactual thrombocytopenia, which occurs when platelets clump in vitro in the presence of the anticoagulant calcium-chelator ethylenediaminetetraacetic acid (usually a purple-top Vacutainer tube). If this clumping is abolished with the use of a citrate-containing solution (usually a blue-top Vacutainer tube), the diagnosis is confirmed.
Tests of Platelet Function

Bleeding time (BT) is typically measured using the Ivy method, in which a sphygmomanometer on the upper arm is used to raise tissue pressure to 40 mm Hg. A standardized 1-mm-deep incision is made in the skin of the anterior forearm. The time it takes for the bleeding to stop is the BT. A normal value is 2 to 9 minutes. The test is still used clinically, but its reliability is considered to be low because its reproducibility is poor.

Accordingly, more standardized automated in vitro methods such as the platelet function analyzer have been introduced. In this test, a machine simulates ex vivo bleeding time by drawing whole blood collected in citrate anticoagulant into two collagen-coated cartridges, which stimulate platelets with collagen and epinephrine (CEPI) or adenosine phosphate. The blood interacts with von Willebrand factor to drive clotting that closes an aperture. If the closure time for epinephrine is less than 180 seconds, platelet function is considered to be normal. If aspirin is present, a normal result implies aspirin resistance. If CEPI is longer than 180 seconds and the closure time for collagen and adenosine diphosphate (CADP) is less than 116 seconds, the most likely cause is the use of aspirin or nonsteroidal anti-inflammatory drugs. If the CEPI is longer than 180 seconds and the CADP is longer than 116 seconds, platelet function is abnormal. A markedly elevated result, such as longer than 300 seconds for both tests, suggests the use of a glycoprotein (GP)IIb/IIIa inhibitor.

All of these tests can provide a preoperative assessment of the adequacy of the conditions for blood clotting. As blood loss occurs in surgery, the tests can be repeated to detect which clotting components are being depleted to the point where they are no longer effective.

Blood Typing and Crossmatching

The membranes of human red blood cells (RBCs) are estimated to contain more than 300 different antigens, and at least 20 different blood group antigen systems have been identified. In most transfusions, only the ABO and Rh antigens play an important role. Patients are at risk for acquiring antibodies to alleles they do not possess (nonself), leading to potentially serious adverse reactions. Almost all individuals produce antibodies to nonself AB alleles by 1 year of age, regardless of their prior exposure. For the Rh antigens, the D antigen is of primary importance. Patients are classified as positive or negative based on the presence of this antigen; 80 to 85% of the population is positive. Rh-negative patients typically develop antibodies only after a transfusion or pregnancy. Transfusion of Rh-positive blood to a man or postmenopausal women is seldom of consequence. Such transfusion is an option in an emergency situation but should be avoided if possible.

Compatibility testing is performed to help avoid a reaction to a transfusion. Testing is performed in the form of screening and crossmatching. The patient’s ABO and Rh type are determined by testing the patient’s blood against serum known to contain antibodies to A, B, and Rh. The results are confirmed by testing the patient’s serum against RBCs with known antigens. Typing can be performed in about 15 minutes.

An antibody screen is designed to detect the most common non-ABO reactions by means of an indirect Coombs test. The patient’s serum is mixed with RBCs with known antigens. If the patient has antibodies to these antigens, the antibodies will coat the RBCs and the addition of antiglobulin antibody will cause agglutination
Blood Loss and Replacement

of the RBCs. Screens require 45 minutes to perform. They are routinely done on all donor blood and can potentially replace a crossmatch for a recipient.

A crossmatch mimics a transfusion in that donor cells are mixed with recipient serum. A crossmatch is able to confirm typing, detect other antibodies, and detect antibodies in low titers not evident on the screen (because they did not agglutinate). Crossmatching provides optimal safety but is reserved for procedures in which a transfusion is anticipated. If the procedure is associated with a transfusion rate of less than 10%, only a type and screen should be performed. A crossmatch-to-transfusion ratio of 2.5:1 is the goal. Ample time and blood should be allocated to allow crossmatching in patients who have undergone prior transfusions, in situations in which multiple transfusions are anticipated, or in patients with known antibodies.2,3

Transfusion-Related Complications

Transfusions are often necessary and can be lifesaving. However, transfusions should be performed judiciously. Adverse events are common, serious, and potentially life-threatening, and the inappropriate use of transfusions is associated with increased rates of morbidity and mortality. Therefore, surgeons should be familiar with the indications and potential consequences, and the potential for adverse reactions should be anticipated. Primary complications are immunity and infection related and include, but are not limited to, acute and delayed hemolytic reactions, transmission of infectious diseases, and development of immune-compromise and coagulopathy.

Acute hemolytic reactions are caused by ABO incompatibility and occur in 1 in 38,000 transfusions. They are typically due to misidentification and result in acute intravascular hemolysis. Patients present with fever, chills, nausea, tachycardia, hypotension, hemoglobinuria, and diffuse surgical oozing. Hemolytic reactions can lead to disseminated intravascular coagulation, shock, and renal failure and are fatal in 1 in 100,000 transfusions. The severity of the reaction often depends on the amount of blood transfused. Barring an emergency, blood products should always be started and infused slowly. Delayed hemolytic reactions occur 2 to 21 days after transfusion, when antibodies develop against less common antigens found in blood products. These reactions are mild and can result in extravascular hemolysis. Non-hemolytic immune complications include fever, urticarial reactions, anaphylaxis, noncardiogenic pulmonary edema, and graft versus host disease. Anaphylaxis occurs in 1 in 150,000 transfusions, most commonly in immunoglobulin A (IgA)-deficient patients.

Transmission of infectious disease is the other major potential complication of blood transfusion. The advent of routine testing for hepatitis and human immunodeficiency virus (HIV) has markedly reduced the transmission rate of these viruses through blood products. The incidence of transfusion-acquired hepatitis C is reported to range from 1 in 60,000 to 1 in 1,900,000 and that for HIV to be 1 in 1,900,000. Cytomegalovirus (CMV) and Epstein-Barr viruses can also be transmitted through this route. Because CMV is capable of mounting a severe infection in immunocompromised patients, these patients should be transfused with CMV-negative units or leukocyte-reduced units.

Bacterial contamination is another potential complication of transfusion and is the second leading cause of transfusion-related deaths. Bacterial contamination is present in 1 in 2,000 platelets and in 1 in 7,000 packed RBCs. Sepsis occurs in 1 in
25,000 platelets and 1 in 250,000 packed RBCs. Prevention measures should include appropriate storage of blood and transfusion within 4 hours of removing the units from storage to ensure the correct temperature. If slower transfusion is desired, the unit should be split.

Blood transfusions are also believed to cause immunosuppression by an unknown mechanism and therefore may increase the risk of serious infection. Massive transfusions are associated with a coagulopathic state, typically from platelet dilution. The patients at highest risk of transfusion-related complications are those who have undergone prior transfusions, the immunocompromised, and those receiving multiple transfusions. A patient who has received previous transfusions is at higher risk for hemolytic, febrile, and urticarial reactions. More time and blood should be allocated to pretesting to ensure appropriate crossmatching. Febrile reactions can be reduced by using leukocyte-reduced packed RBCs. Leukocyte-reduced cells can help lower the risk of infection, and irradiated cells can help prevent graft versus host disease, particularly in immunocompromised patients who are at higher risk. Massive blood transfusion is also associated with unique risks, including coagulopathy, hypocalcemia, and hypothermia. In patients receiving one or two times their circulating blood volume, preparation should be made to transfuse platelets and fresh frozen plasma (FFP), and all blood products and fluids should be warm.

Intraoperative Assessment of Blood Status and Volume Replacement

Maintaining proper fluid balance is critical during anesthesia. Preoperative fluid deficit, maintenance of fluid requirement, and replacement of ongoing fluid losses should be considered. Maintenance of fluid requirement is typically estimated as 100 mL/kg/day for the first 10 kg of body weight, 50 mL/kg/day for the next 10 kg, and an additional 20 mL/kg/day for each kg over 20 kg. Surgical patients enter surgery with a fluid deficit from their preoperative fast, and this deficit must be replaced. For the average 70-kg adult, fasting for 8 hours amounts to an 880 mL loss in fluid. Once surgery has begun, fluid loss is accelerated due to surgical blood loss, wound exposure, and tissue trauma. Most neurosurgical procedures are associated with only a small amount of evaporative fluid loss; however, evaporative loss can become significant during long spinal procedures involving large wounds and extensive tissue trauma.

Fluid status and blood loss must be assessed and corrected constantly. Vital signs, urine output, estimated blood loss, and laboratory data must be monitored closely. Unfortunately, the volume of blood loss can be difficult to estimate given that considerable blood can be lost under surgical drapes and in sponges and due to calculation errors incurred by the contribution of irrigation fluid.

Volume replacement should precede the development of hypotension and tachycardia, two physiological signs of the body's response to volume depletion. A drop in urine output is a useful sign of hypovolemia. An adult should maintain a urine output of 0.5 to 1.0 mL/kg/hour. The base deficit can also indicate the volume status and adequacy of replacement. Serial evaluations of the hematocrit can be followed to assess blood loss. However, because the hematocrit level reflects the ratio of blood cells to plasma rather than blood loss, results can be affected by fluid shift and intravenous replacement. Therefore, clinical status and the estimated blood loss should take precedence.
Fluid replacement should begin with the administration of isotonic crystalloid solutions. In many specialties the first fluid given is lactated Ringer's solution. However, this solution is actually slightly hypotonic and lowers serum sodium. Therefore, it is not the preferred solution for neurosurgical procedures, especially for cranial pathology or in the setting of head trauma. Normal saline is the preferred alternative because of its high sodium content and relative hyperosmolality, both of which reduce brain volume and therefore intracranial pressure. Normal saline given in large volumes produces a hyperchloremic metabolic acidosis, which produces a compensatory respiratory alkalosis. This hypocapnia, in addition to the higher sodium content, may be desirable in the setting of head trauma to treat intracranial hypertension. However, caution is needed in patients with subarachnoid hemorrhage, in whom excessive hypocapnia can exacerbate vasoconstriction. Glucose-containing fluids should be avoided in neurosurgical patients because hyperglycemia can increase the deleterious effects of an ischemic brain injury.

The timing and indications for colloid solutions (e.g., serum albumin) are not well established. Administration of colloid solutions is usually considered after 3 to 4 L of crystalloid solution have been administered with an inadequate hemodynamic response. Colloid solutions are typically administered in a 3–4:1 ratio to blood loss. Colloid solutions correct fluid deficits more rapidly than crystalloid solutions, have an intravascular half-life of 3 to 6 hours, and are less frequently associated with significant tissue edema. The effective osmoles in colloidal fluids are larger and therefore are less likely to leach into the interstitial space, which is believed to be the reason for the reduction in edema. Tissue edema can impair oxygen delivery and tissue healing. Because prevention of tissue edema and poor oxygenation is critical in neurosurgery, particularly in the case of head trauma, some neurosurgeons favor colloid use for fluid replacement.

Despite its desirable features, colloid use is limited by its cost and potential complications. Colloids are derived from either plasma proteins or synthetic glucose polymers in an isotonic solution. Blood-derived colloids include albumin and plasma protein fraction and carry a risk of viral transmission and a hypotensive allergic reaction. Synthetic colloids include gelatins (not available in the United States) and dextrose starches. Dextrans are associated with antiplatelet effects, renal failure, and mild-to-severe anaphylactic reactions. Hetastarch is a highly effective plasma expander that is rarely associated with anaphylactic reactions or negative effects on coagulation status.

### Blood Factor Replacement

Whole blood is seldom administered for replacement, except in massive transfusion protocols. Instead, individual blood components are administered depending on the perceived deficit the patient is suffering. This section reviews general protocols and indications for blood product transfusion and then presents concerns specific to cranial and spinal surgery.

### Packed Red Blood Cells

The RBCs are used to increase oxygen-carrying capacity during blood loss and profound anemia in the setting of impaired oxygen delivery. One unit of packed RBCs
(pRBCs) has a hematocrit of 55 to 80% and a volume of 250 mL. In a 70-kg male, a single unit can be expected to raise hemoglobin by 1 g/dL and the hematocrit by 3%. This amount is usually physiologically inconsequential; therefore, at least two units of pRBCS are typically administered at a time.\(^5\)

Given the considerable risks of both over- and undertransfusion, considerable effort has been exerted to determine the appropriate indications for transfusion. This effort led to the development of a Task Force on Blood Component Therapy by the American Society of Anesthesiologists. The Task Force concluded that transfusion should not be dictated by a single hemoglobin level; rather, it should be based on the individual patient’s risk of developing complications related to inadequate oxygenation. In most instances, the Task Force found that transfusion was indicated for a hemoglobin level < 6 g/dL and was rarely needed for hemoglobin levels > 10 g/dL.

Carson et al\(^6\) published a meta-analysis of six studies comparing liberal and restrictive transfusion trials. They analyzed complete transfusion outcome and 30-day mortality rates in 1,568 patients. The liberal transfusion group had a mean transfusion trigger of 9.7 mg/dL of hemoglobin and received 4.4 units of RBCs. The conservative group had a mean transfusion trigger of 7.5 mg/dL of hemoglobin and received an average of 2.3 units of RBCs. There were 120 (15.2%) deaths in the liberal group compared with 94 (12%) in the conservative group, suggesting that the incidence of adverse events is lower with restrictive transfusions than with liberal transfusion. The incidence of cardiac events was not affected.\(^7\)

The type of neurosurgical pathology and type of patient may affect the decision to transfuse. In patients with subarachnoid hemorrhage, a target hematocrit of 30 mg/dL is often accepted as a good balance between dilute enough to promote flow through optimum rheology and concentrated enough to deliver adequate oxygen to the brain. In contrast, the hematocrit level of a spine surgery patient with a history of coronary ischemia and whose hematocrit level is borderline immediately after surgery may need to be kept higher to prevent a drift into a clinically significant anemia.

**Platelets**

Platelets are transfused prophylactically to prevent bleeding or for therapeutic replacement in thrombocytopenic patients with active bleeding. Platelets come as pheresis-collected single donor units containing 3 to \(6 \times 10^{11}\) platelets each. They can also be collected from the whole blood of six different donors containing an average of \(7.5 \times 10^{10}\) platelets in each pack. Single donor platelets are preferred, because they are associated with a lower rate of disease transmission and less potential to drive an allergic response. Transfusion of one single donor unit of platelets is expected to raise the platelet count by 50,000/mm\(^3\). This response, however, is variable. Laboratory values should be followed to assess the actual amount of platelet correction.

Increased platelet consumption, active thrombosis, destruction by platelet antibodies, and splenic sequestration can blunt the expected platelet response. Importantly, the cause of thrombocytopenia should be considered when deciding to transfuse. In platelet-consumptive conditions, the available platelets are typically younger, larger, and better functioning, thereby reducing the need for transfusion. Patients with platelet hypoplasia and comorbid conditions are more likely to require a transfusion.
The Task Force recommended prophylactic platelet transfusion for surgical patients or patients with microvascular bleeding with platelets < 50,000/mm³, and for high-risk surgical patients with or without microvascular bleeding, with platelets between 50,000 and 100,000/mm³. The Task Force does not recommend routine prophylactic transfusion for thrombocytopenia related to platelet destruction, for minor procedures or surgeries associated with insignificant blood loss, or for surgical patients with platelet counts > 100,000/mm³. They also noted that platelet transfusion may be necessary for patients with normal platelet counts but known platelet dysfunction and microvascular bleeding.

**Fresh Frozen Plasma**

One unit of FFP contains 200 to 250 mL of volume, 1 unit of each coagulation factor, and 2 mg of fibrinogen per milliliter. A unit of FFP has an INR of 0.9 to 1.2 and correction with FFP should not be expected to lower a patient’s INR below 1.2 to 1.3. FFP takes 20 to 40 minutes to thaw, and this process cannot be accelerated. The Task Force recommends transfusion of FFP for urgent reversal of warfarin, for correction of known factor deficiencies when specific factors are unavailable, for correction of microvascular bleeding with PT or PTT over 1.5 times normal, and for patients with microvascular bleeding who have received a massive transfusion (≥ 12 units PRBC).

**Cranial Surgery**

Given the brain’s sensitivity to oxygen deprivation and the potentially devastating consequences of uncontrolled bleeding in neurosurgical patients, blood replacement in cranial procedures requires special consideration. Weiskopf et al found that cognitive functioning is compromised at hemoglobin values less than 6 mg/dL. This study was performed in healthy volunteers; many believe that the injured brain is susceptible to anemia at even higher hemoglobin levels. Animal and human studies have shown worse outcomes in anemic patients who suffer a traumatic brain injury. However, transfusion has not been shown to improve their outcomes.

Unfortunately, no adequate studies are available to guide transfusion triggers in the neurosurgical population. However, it is reasonable to believe that transfusion strategies applicable to other patients may not be most appropriate for the neurosurgical population. Further research is needed to determine the optimum hemoglobin target for a transfusion of RBCs in patients with central nervous system (CNS) pathology.

Platelet and factor replacement is also unique in neurosurgical patients, given the high risk of bleeding complications and coagulopathic state that often accompanies CNS disease. Patients undergoing neurosurgery or those suffering from intracranial hemorrhage usually receive transfusions when their platelet count is less than 100,000/mm³. Platelets in patients with a brain injury may not function normally. Ongoing microvascular bleeding despite normal platelet counts should prompt consideration of transfusion.
Spinal Surgery

Spinal surgery can often be extensive and result in considerable blood loss. Anticipation of these factors provides the opportunity to use transfusion-conservation strategies, such as cell saver and normovolemic hemodilution. Close attention should be paid to blood loss during surgery, pursuing meticulous hemostasis wherever possible. As larger cases progress, regular review of the status of blood loss with the anesthesia team, as well as communicating future anticipated blood loss, can facilitate proactive strategic replacement. Finally, for cases of extreme blood loss involving an entire volume of blood or more, the option of staged surgery is a reasonable consideration.

Intraoperative Cell Salvage

Intraoperative cell saver, or autologous blood salvage, is often used in surgeries when a large volume of blood loss and the need for blood transfusion are anticipated. The most appropriate use in neurosurgery is in clean non-oncological cases where considerable blood loss is common (e.g., large spine surgeries), rather than in cases where large volume blood loss is possible but infrequent (i.e., aneurysm repair). Cell saver circumvents the risk of adverse effects from an allogenic blood transfusion and may be accepted by patients who refuse exogenous transfusions due to religious beliefs.

Three types of cell savers are available: RBC savers, direct transfusion, and ultrafiltration of whole blood. Cell processors or RBC savers centrifuge intraoperatively salvaged blood. RBCs are washed and separated, whereas platelets, plasma proteins, clotting factors, and by-products such as cytokines, anaphylatoxins, and additional waste products are removed. In a direct transfusion, blood is transferred through an extracorporeal circuit, typically during cardiopulmonary bypass surgeries, collected, and then re-infused. This blood tends to be more dilute (hemoglobin 6–9 g/dL) and contains cytokines and other waste products that have been implicated in organ dysfunction and edema. The third type, ultrafiltration of whole blood, removes excess noncellular plasma water, solutes, particulate matter, and waste substances, and re-infuses whole blood. It includes platelets, clotting factors, and plasma proteins and typically retains a normal level of hemoglobin. During blood recovery, many commonly used hemostatic agents should be avoided to prevent clotting within the recovery circuit. Studies are needed to compare the efficacy of various cell salvage techniques in replacing intraoperative blood loss in neurosurgical patients.12–14

Normovolemic Hemodilution

Normovolemic hemodilution is based on the principle that reducing the concentration of RBCs leads to a reduction in the total number of RBCs lost during large volume blood loss and that cardiac output remains normal when intravascular volume is maintained. The process begins with the controlled removal of one to three units of whole blood, depending on the level of the preoperative hematocrit, to target a hematocrit of 28%. The blood volume removed is replaced with three to four times the volume of crystalloid or colloid solution. The blood is then transfused when needed.
A study involving adolescents undergoing correction of scoliosis showed a reduction of allogeneic transfusion from 79% to 37% using normovolemic hemodilution. Another study in patients undergoing lumbar fusion showed an allogeneic transfusion rate of 23.5%, whereas a group in a comparable study had a rate of 40%. Given the aforementioned concerns with allogeneic transfusion, such a drastic reduction could have a profound impact on patient outcomes.\textsuperscript{15} Again, this kind of conservation strategy makes the most sense in procedures such as spine surgery to correct a deformity, where significant blood loss is almost certain.

**Blood Replacement in the Jehovah’s Witness**

Some patients will not accept blood product transfusion because of their religious beliefs. In North America, the most common group encountered is the Jehovah’s Witnesses, who refuse blood transfusions on the premise that several biblical passages state that blood cannot be eaten as “nourishment.” As a group, Jehovah’s Witnesses typically will not accept whole blood, RBCs, platelets, plasma, or stored autologous blood. Acceptance of the following products varies on an individual basis: plasma proteins (albumin, cryoprecipitate, immunoglobulin), stem cells, autologous blood preserved in a cell saver, clotting factors, bone marrow transplants, organ transplants, epidural blood patches, and extracorporeal circulation (dialysis, plasmapheresis, cardiac bypass machines).

Correcting anticoagulation or controlling acute bleeding is a challenge in these patients, and physicians must be aware of and use strategies to minimize perioperative blood loss, to optimize hemodynamics, and to increase blood production. The strategies used can be applied to all neurosurgical patients.

Perioperative blood loss can be limited by conducting phlebotomy only when necessary, by using pediatric sample tubes (can decrease blood volume drawn 40–45% compared with conventional tubes), by increasing point-of-care testing, and by using the appropriate medication to prevent bleeding (e.g., desmopressin and aprotinin). The neurosurgeon should strongly consider optimizing RBC mass and production before surgery via nutritional supplementation with vitamin B\textsubscript{12}, folate, and iron (intravenous route acts much more quickly), and a nutritional consultation should be considered.\textsuperscript{16,17}

Erythropoietic stimulating agents such as erythropoietin may help, depending on the acuity of blood loss. Some studies have shown a decrease in transfusion requirements when erythropoietic stimulating agents are administered in the acute setting.\textsuperscript{18,19} However, these agents are not a replacement for transfusion, because there is still a delay of several weeks between the administration of erythropoietin and the production of new RBCs.\textsuperscript{20} Careful preoperative planning involves possible angiographic embolization, staged operations, and selection of minimally invasive procedures. Plans for careful dissections and vigilant coagulation of all bleeding, regardless of how minor, are crucial for these patients.\textsuperscript{21}

Hemodynamic parameters may be maximized by increasing oxygen content, by optimizing cardiac output, and by lowering the patients’ metabolic rate. Blood substitutes such as hemoglobin-based oxygen carriers have been studied as an alternative to blood transfusion. No blood substitute has been approved by the US Food and Drug Administration in the setting of acute bleeding. The three drugs (HemAssist, PolyHeme, and Hemopure) that have reached phase 3 trials did not decrease transfusion requirements during surgery and were associated with significant adverse events, including increased risk of myocardial infarction.
and death.\textsuperscript{22–24} Infusion with crystalloid solutions to maintain circulating volume remains the standard of treatment in these patients when they experience decreased cardiac output and decreased blood volume during surgery.\textsuperscript{16}

**Conclusion**

Management of intraoperative blood replacement requires careful assessment of the patient’s preoperative, operative, and postoperative hemodynamic and coagulation status. When appropriate, blood product transfusion should be used judiciously, with consideration of the potentially devastating complications that can ensue. Care should be taken to investigate and address the cause of all blood component deficiencies.

Adequate fluid status must be maintained during surgery. Colloid solutions restore volume deficits more rapidly than do crystalloids and are less likely to induce tissue edema. It is, however, more costly, and it is associated with complications of its own. When crystalloid solutions are used, normal saline is preferred, because its isotonic fluid balance and higher sodium content help prevent cerebral edema and further brain injury.

Finally, in surgeries where high volume blood loss is foreseen (e.g., extensive spinal operations) or barriers to adequate blood and volume replacement are anticipated (e.g., Jehovah’s Witnesses), various blood conservation measures must be used. These measures include cell saver, normovolemic hemodilution, nutritional and medical optimization of RBC production, logistical considerations to decrease iatrogenic blood loss, and careful surgical planning to minimize blood loss.

**KEY POINTS**

- The INR and PTT are used clinically to assess coagulation function and follow anticoagulant therapies.
- A normal platelet count does not guarantee normal platelet function.
- Platelet counts $< 100,000 \times 10^9$ should alert the physician to potential challenges with intraoperative control of bleeding.
- A normal value for bleeding time is 2 to 9 minutes.
- Aspirin, nonsteroidal inflammatory agents, and clopidogrel alter platelet function.
- Blood typing and blood crossmatch processes facilitate a low transfusion risk for patients.
- However, transfusion-related complications may include acute and subacute hemolytic reactions, anaphylaxis, transmission of infectious disease, bacterial contamination, immunosuppression, febrile reactions, graft versus host disease, hypocalcemia, hypothermia, and coagulopathy.
- Intraoperative assessment of blood volume requires determination of a patient’s preoperative volume status, monitoring of physiological parameters, and monitoring of the blood losses during surgery.
- The intraoperative hematocrit may not be a reliable measure of blood loss if large volumes of crystalloid or colloid solution have been used.
- A single unit of pRBCs will raise the hemoglobin by about 1 g/dL and the hematocrit by 3%.
- Preoperative, intraoperative, and postoperative transfusion triggers should be determined for patients.
A single donor unit of platelets transfused will raise the platelet count by about 50,000/mm$^3$.

One unit of FFP has a volume of 200 to 250 mL and an INR of 0.9 to 1.2.

Cell savers have a role in elective, nontumor surgery when a large volume of blood loss is expected.

Normovolemic hemodilution can be a useful preoperative strategy when a large volume of blood loss is expected.

Nutritional and medical optimization of RBC production may have a role when planning elective surgery in high-risk patients.

**REVIEW QUESTIONS**

1. True or false:
   - A. An international reference standard is used to calculate the INR.
   - B. The INR is abnormal for all clotting disorders.
   - C. The INR is used to monitor the clotting potential with heparin therapy.
   - D. An INR value of 1.2 is abnormal.
   - E. The INR assesses vitamin K–dependent factors.

2. True or false:
   - A. The normal range for the platelet count is 60–700 × 10$^9$/L.
   - B. A normal platelet count ensures a normal bleeding time.
   - C. Spontaneous bleeding may occur with a platelet count less than 20 × 10$^9$/L.
   - D. A normal bleeding time is 9 to 12 minutes.
   - E. Aspirin can increase bleeding time.

3. True or false:
   - A. Blood compatibility testing uses antibodies A, B, O and Rh.
   - B. Blood typing typically takes < 5 minutes to perform.
   - C. An additional antibody screen for non-ABO reactions utilizes an indirect Coombs test.
   - D. A crossmatch mimics a transfusion by mixing donor and recipient cells.
   - E. A failed crossmatch is associated with agglutination of the mixed blood types.

4. Regarding acute hemolytic reactions, true or false:
   - A. They occur during 1 in 75,000 transfusions.
   - B. They are caused by Rh incompatibility.
   - C. They produce intravascular hemolysis.
   - D. They are fatal in 1 in 100,000 transfusions.
   - E. Patients may present with fever, chills, nausea, tachycardia, hypotension, and hemoglobinuria.

5. Regarding intraoperative assessment/treatment of blood status and volume, true or false:
   - A. The average fluid deficit after an 8-hour fast for a 70-kg male is 500 mL.
   - B. An adult should maintain a urine output of 0.5 to 1.0 mL/kg/hour.
   - C. The hematocrit is a reliable measure to reflect blood loss.
   - D. Volume replacement should precede the development of hypotension and tachycardia.
   - E. Fluid replacement should begin with a colloid solution.
6. True or false:
   A. One unit of packed red blood cells (pRBCs) has a hematocrit of 55 to 80% and a volume of 250 mL.
   B. A single unit of pRBCs will raise the hemoglobin by 2 g/dL and the hematocrit by 6% in a 70-kg male.
   C. Single-donor platelet units have a platelet count of $3\times 10^6$.
   D. A single unit of platelets will raise the platelet by 50,000/mm$^3$ in a 70-kg male.
   E. A unit of fresh frozen plasma has an INR of 0.9 to 1.2, takes 20 to 40 minutes to thaw, and should not be expected to lower a patient's INR below 1.2 to 1.3.

References


**ANSWER KEY**

1. A: True; B: False; C: False; D: True; E, True
2. A: False; B: False; C: True; D: False; E, True
3. A: False; B: False; C: True; D: True; E, True
4. A: False; B: False; C: True; D: True; E, True
5. A: False; B: True; C: False; D: True; E, False
6. A: True; B: False; C: False; D: True; E, True
The transfusion of blood products in the perioperative setting is often necessary to provide adequate tissue oxygenation and to maintain hemostasis.\textsuperscript{1-3} The benefits of these transfusions, however, need to be balanced against the risks of hemolytic and febrile transfusion reactions, volume overload, transfusion-related acute lung injury (TRALI), immunosuppression, intravascular thrombosis, and transmission of infectious agents. The appropriate use of transfused blood products relies upon recognition of these risks and benefits and an understanding of the collection, preparation, and storage of blood components, and their biochemistry.

Collection, Processing and Storage of Donated Blood

Units of blood collected for use in the United States are exclusively obtained from volunteer donors.\textsuperscript{4} The donated units are ABO and Rh typed and screened for infectious agents including bacteria, syphilis, hepatitis B and C, human immunodeficiency virus (HIV) 1 and 2, human lymphocytotropic virus (HTLV) 1 and 2, West Nile virus, and \textit{Trypanosoma cruzi}. In addition, the level of alanine aminotransferase is measured as a surrogate marker for hepatitis. In the future, screening for other blood-borne pathogens or exclusion of donors may be required, because of immigration from areas where malaria and other blood-borne infections are prevalent. For example, donors who have lived in the United Kingdom for more than 3 months between 1980 and 1996 are excluded from blood donation due to the theoretical risk of transmission of bovine spongiform encephalopathy.

Red blood cells are stored at 1° to 6°C in the acid-citrate-dextrose (ACD) or citrate-phosphate-dextrose (CPD) solution to which adenine, glucose, and mannitol have been added. Under these conditions, the red blood cells (RBCs) are suitable for transfusion for up to 6 weeks.\textsuperscript{5} Older units of RBCs may have a shorter survival in recipients, and may be less efficient in oxygen exchange; however, there are no clear-cut recommendations regarding the use of older versus newer RBC units.\textsuperscript{6} In some instances, units of RBCs can be frozen in a glycerol solution and stored for longer periods of time.

Leukodepletion and Irradiation

Since 1996, filtration of blood at the site of collection has been mandated as a means of reducing white blood cell contamination of blood products. The contamination of blood products by white blood cells (principally lymphocytes) and their
products increases the risk of febrile nonhemolytic transfusion reactions by the passive transfer of cytokines released during the processing and storage of blood. Contaminating leukocytes can sensitize the recipient to human leukocyte antigens (HLAs) and generate antibodies that will shorten the survival of transfused platelets, leading to shortened survival of the transfused cells. In addition, lymphocytes containing cytomegalovirus (CMV) can infect a seronegative recipient and produce clinically significant pneumonia, colitis, hepatitis, or retinitis, particularly if the recipient is immunosuppressed.7,8 In severely immunocompromised patients, such as those receiving chemotherapy, radiation therapy, bone marrow and solid organ transplant, or potent immunosuppressive agents, viable lymphocytes from the donated blood product (usually RBCs or platelets) may engraft and cause fatal graft-versus-host disease (GVHD). The symptoms of GVHD include skin eruptions, diarrhea, fever, thrombocytopenia, and hepatic dysfunction. This complication can be prevented by irradiation of the blood products prior to transfusion to render any contaminating lymphocytes incapable of proliferation.9

Platelet Donation

As noted above, the need for filtration leukoreduction for all units of donated blood has made the collection of platelet concentrate from individual blood units difficult. Many transfusion departments exclusively collect platelets by apheresis from volunteer donors. A donor can provide about $3 \times 10^{11}$ platelets per treatment, which is the equivalent of four to six units of platelets prepared from single units of blood. The higher costs of this method of collection is offset by the potential benefits of reduced exposure of the recipient to multiple donors, reduced risk of HLA sensitization, improved platelet survival, and the potential for HLA matching of donors with patients who are refractory to transfusion.10 If the recipient has not received a blood transfusion or has not been pregnant within the past 3 months, often electronic crossmatch can be performed because the risk of clinically significant antibodies would be low. In other instances, a screen for alloantibodies may be necessary to prevent an immediate or delayed hemolytic transfusion reaction. It is important to note, however, that most instances of clinically significant transfusion-associated hemolytic episodes are not due to minor blood group antigen incompatibility. Instead, errors in patient identification and specimen labeling of the type and screen at the bedside are responsible for these potentially lethal events.11

Red Blood Cell Transfusions

The transfusion of one unit of packed RBCs, which contains a hematocrit of ~ 0.70 and a volume of ~ 225 mL, should increase the hemoglobin by 1 g/dL and hematocrit by 0.03. Although the increment of hemoglobin following the transfusion of units of RBCs is well known, the criteria for their use in the perioperative setting have changed in the past decade as the indications for transfusions have become more rigorous. The traditional recommendation of maintaining a hemoglobin concentration of 10 g/dL and hematocrit of 0.30 for patients undergoing surgery has been critically challenged.12–16 A series of studies evaluating the risks and benefits of restriction of RBC transfusions in cardiac and orthopedic surgery have demonstrated that patients undergoing surgery with hemoglobin concentrations of greater than 10 g/dL do not require transfusions, whereas those with hemoglobin concen-
trations of less than 7 g/dL will benefit from this intervention. Bracey et al performed a randomized controlled trial of 428 patients undergoing coronary artery bypass surgery in which patients were transfused at hemoglobin concentrations of either less than 9 g/dL or 7 g/dL. Although the rate of transfusion was higher in those patients allocated to the higher hemoglobin goal, outcomes including fatigue scores, morbidity, and mortality, were similar in both groups. This study also indicated that the use of blood transfusions for patients with hemoglobin concentrations that were greater than 8 g/dL did not reduce perioperative mortality. These studies have also suggested that the risk of infection and prolonged hospitalization was associated with more liberal use of RBC transfusion.

Hébert et al studied 838 critically ill euvolemic, nonsurgical patients, and randomly assigned 418 to a restrictive transfusion strategy that maintained the hemoglobin between 7 and 9 g/dL compared with patients maintained at hemoglobin concentrations at 10 to 12 g/dL. In the subgroup analysis of the study, patients who were less ill (Acute Physiology and Chronic Health Education [APACHE] II score ≤ 20) and younger had better outcomes with a more restrictive transfusion protocol. Conversely, patients with a history of angina or congestive heart failure did worse with the more restrictive criteria for transfusion. The conclusions that were derived from this study were that rather than relying upon a fixed target hemoglobin, the patient’s overall cardiovascular function needs to be assessed, and RBC replacement adjusted accordingly. Similar conclusions have been reached by meta-analyses of clinical trials of patients undergoing elective surgical procedures.

The advantage of more liberal or restrictive transfusion policies in neurological patients is less clear. Flückiger et al observed that acute resuscitation of patients with traumatic brain injury to a hematocrit of 0.28 was associated with improved outcomes. There are contrasting results regarding the optimum transfusion goal in patients with subarachnoid hemorrhage (SAH) and patients with intracerebral hemorrhage (ICH). Although arterial blood flow may be favored by a lower hemoglobin concentration and blood viscosity, this might be at the expense of tissue oxygen delivery. Naidech et al studied the effects of hemoglobin concentration in a retrospective study of 103 patients with SAH. Univariate analysis showed that a high hemoglobin concentration on day 0 and day 1 following the SAH predicted a better clinical outcome. Serial determinations of hemoglobin concentration also showed that SAH survivors had consistently higher values during their hospital course. A similar conclusion was reached by Sheth et al, who retrospectively reviewed 546 patients with nontraumatic ICH. These investigators noted an improved 30-day survival in patients receiving RBC transfusions compared with nonanemic, nontransfused patients. Unfortunately, in neither of these studies was there a consistent hemoglobin concentration that triggered the decision for transfusion. Thus, precise recommendations of optimum hemoglobin concentration in ICH and SAH remain elusive.

Although most reviews of blood use in neurosurgery indicate that many more units are screened and prepared than are used, preoperative and intraoperative measures are available to further reduce the need for allogeneic blood transfusion. Preoperative treatment of the elective patient with erythropoiesis-stimulating agents (ESAs, darbepoetin and erythropoietin) have been proposed as a means of raising the hemoglobin concentration and enabling the patient to provide autologous blood for use during surgery. Although this approach has been widely used in orthopedic surgery (including spine surgery) and had been shown to reduce use of allogeneic transfusions, its application to neurosurgery is less clear. In addition, the use of ESAs has been associated with an increased risk of
thrombosis; thus, this approach may be undesirable in neurosurgical patients who are already at increased risk of thrombotic events.

**Platelet Transfusion**

Thrombocytopenia in the neurosurgical patient poses a unique problem because hemorrhage, which would be considered trivial in abdominal, cardiovascular, or gynecologic surgery, may be catastrophic following procedures in the axial or peripheral nervous system. Unfortunately, there is no evidence-based information to determine a “safe” level of platelet count prior to neurosurgery. Several consensus statements have chosen a value of 100,000/µL as a minimum platelet count; however, the patient’s risk of hemorrhage is affected not only by the number of platelets but also by their function. A patient with a platelet count of 200,000/µL who has been treated with aspirin or clopidogrel is at a much greater risk of bleeding than a patient with immune thrombocytopenia and a platelet count of 80,000/µL. Consequently, decisions regarding platelet transfusion in the neurosurgical patient need to be based on the complete medical history.

Patients with a platelet count less than 100,000/µL who require neurosurgical intervention will usually receive platelet transfusions. One unit of apheresis platelets will increase the platelet count in a patient with normal clearance of platelets by 40,000 to 60,000/µL. The efficacy of this replacement can be reduced by the presence of platelet alloantibodies (which might develop in multiply transfused patients such as those requiring transfusions during the course of chemotherapy or bone marrow failure) or by intravascular consumption due to disseminated intravascular coagulation or thromboses. Drug-induced thrombocytopenia might also lead to reduced survival of transfused platelets. Consequently, the adequacy of the response to platelet administration should be documented within 1 to 2 hours following transfusion to ensure adequate hemostasis during and following a surgical procedure. Even with normal platelet survival, the need for additional platelet transfusions should be anticipated. The platelet count should be maintained at greater than 100,000/µL for at least 48 to 72 hours following a neurosurgical procedure, and greater than 50,000/µL for the next 7 days. Radiographic follow-up for evidence of hemorrhage into the operative site is prudent even with maintenance of an adequate platelet count.

**Autologous and Directed Donation**

Since the advent of the HIV epidemic, patients and physicians have sought to limit exposure to allogeneic units of blood. Two commonly employed approaches are directed donations and autologous donations. With autologous blood donation, the patient donates one to two units of whole blood prior to elective surgical procedure. As noted above, ESAs may be employed; however, the safety of their use has been questioned. The advantage of this approach is the ability to replace RBCs and plasma volume with a product that does not entail the risks of transmission of disease, transfusion reaction, or alloimmunization. The autologous donation programs place a burden on the transfusion service, as they require separate record keeping, a guarantee that the autologous units are administered to the appropriate patient, and the development of a policy for disposition of units not used
during surgery. This last point is surprisingly complex; often patients are discharged from the hospital following surgery without using the autologous units, only to wind up needing them several days later. The blood bank needs to be certain that the units are not disposed of (either by wasting them or administering them to another patient) before determining that the donor is no longer in need of them. An additional complication ensues when the patient might be otherwise ineligible to donate blood due to HIV or hepatitis B or C infection. These units need to be strictly quarantined from the remainder of the blood supply, and management of these blood products places an additional administrative and medicolegal burden on the transfusion service.

Directed Donations

Directed donation of blood products are often requested by patients with the belief that products from friends or family members are inherently safer than those obtained from volunteer donors. Epidemiological and serological studies of the risks of transfusion-associated disease have shown no difference in the rates of HIV infection and hepatitis B and C infection among directed donors compared with the general donor population. In addition, ABO or Rh incompatibility may make the directed donations of RBCs useless for the intended patient. Direct donations of single-donor apheresis platelets can be useful in supplementing the supply of blood products, particularly in patients who, due to alloimmunization and prolonged myelosuppression, may have a prolonged need for platelet transfusions. In general, however, directed donations should be discouraged if their use is based on the perception of greater safety of the blood products from the recipient’s friends and family members.

Blood Conservation Strategies in the Treatment of Jehovah’s Witnesses

Jehovah’s Witnesses refuse the administration of blood products on religious grounds. Generally, patients whose religious principles lead them to avoid blood products are sophisticated regarding the consequences of this refusal; release forms describing the risks of not accepting blood products are usually available in most health care facilities and may help to absolve the physician of a poor outcome due to severe anemia or bleeding.

The magnitude of the risk of refusal of blood has been reported by Carson et al in patients undergoing abdominal, orthopedic, or neurosurgical procedures. The 30-day mortality following a variety of surgical procedures was 0% when patient’s postoperative hemoglobin was 7.1 to 8.0 g/dL. This mortality rate rose to 30% with the postoperative hemoglobin concentrations of 3.1 to 5 g/dL and to 64% with hemoglobin concentrations of 3 g/dL or less.

The experience of neurosurgery without the use of blood products was reported by Suess et al, who described cranial and spinal neurosurgical procedures in 103 Jehovah’s Witness patients compared with 515 control patients. Surgical hemostasis was maintained with electrocautery and topical hemostatic agents, and volume expansion was maintained only with crystalloids and colloids. A cell saver was used in 34% of the patients undergoing spine surgery. Interestingly, the blood
Blood Loss and Replacement

loss from the 103 Jehovah’s Witness patients was 34.5% less than from the control group, although their length of hospitalization was 15% longer than that of the controls.38

The management of patients who refused to accept blood transfusions includes the use of ESAs to raise the hemoglobin prior to surgery, the use of RBC sparing, the use of procedures such as cell savers during the course of the surgery, and the potential use of blood substitutes. The use of erythropoietin prior to surgery may require several weeks to obtain an optimal response. Consequently, elective procedures should be planned well in advance. The postoperative administration of erythropoietin will also have a delayed onset of effect. As noted earlier, the use of these medications may be associated with the risk of thrombosis, and consequently these risks should be considered in formulating a treatment plan.

The use of cell savers to scavenge blood from the operative field has been widely used in abdominal, thoracic, and orthopedic surgery.24,39 It should be noted, however, that Jehovah’s Witness patients usually accept the use of this device only if the blood circuit is completely closed, and there is no offline processing of the blood products.

Blood Substitutes

Blood substitutes have been in development for over 80 years, but no truly satisfactory product has become commercially available. Initial attempts with the use of fluorinated hydrocarbons were unsuccessful due to the low oxygen-carrying capacity of these molecules and the risk of thrombosis, including stroke and myocardial infarction.40 The use of stroma free hemoglobin has been investigated in patients requiring blood resuscitation following trauma.41,42 The use of these products has also been complicated by the risk of thrombosis, vasoconstriction, and hypertension, probably mediated by the ability of the hemoglobin to antagonize the vasodilatory effect of nitric oxide.43 In addition, unmodified stroma free hemoglobin is rapidly cleaved into dimers and cleared by glomerular infiltration; this property may contribute to the nephrotoxicity of this form of hemoglobin. Because the free hemoglobin is not bound to 2,3-diphosphoglycerate as in an intact RBC, it has a higher affinity for oxygen and is less efficient in its release of oxygen to the tissues. Modifications of the hemoglobin molecule, including polymerization and internal cross-linking, may reduce the nephrotoxicity and improve the tissue oxygen delivery.43 Case reports of the compassionate use of a polymerized bovine hemoglobin oxygen carrier (HbOC-1, Hemopure, Biopure Corporation, Cambridge MA) in patients with sickle cell anemia, hemorrhage, acute leukemia, and hemolytic anemia have been reported, with six of eight patients surviving.44 Complications included hypertension, thrombosis, and methemoglobinemia. Thus, although these products may have some benefit in an emergency, they remain investigational.

Plasma Components

Fresh Frozen Plasma

Fresh frozen plasma is isolated from donated blood and stored at −18° to −30°C; it has a shelf life of at least 1 year. The principal use of this product is to replace
coagulation factors in situations where coagulation factor concentrates are not available, to treat patients with multiple coagulation factor deficiencies (i.e., liver disease), to acutely reverse warfarin anticoagulation, to treat thrombotic thrombocytopenic purpura, to replace rare plasma protein deficiencies (C-1 esterase inhibitor, congenital thrombotic thrombocytopenic purpura [TTP]), and to treat patients requiring massive transfusion with RBCs and crystalloid. The usefulness of FFP in replacing coagulation factors is limited by the low concentration of the coagulation factors relative to their need for hemostasis. For example, 1 mL of FFP contains one unit of factor VIII (FVIII) activity. A patient with severe hemophilia A (FVIII level of < 1%) requires a level of about 78 to 80% to safely undergo a surgical procedure. The patient's plasma volume can be calculated as (Weight [kg] × 70 mL/kg) × (1-Hematocrit). Thus, for a 70-kg patient with a hematocrit of 45, the plasma volume will be 2695 mL, and 2156 mL of plasma (or ~ 9 units) will be needed to supply the requisite coagulation factor activity. In so doing, however, the plasma volume will be almost doubled, leading to dilution of the net coagulation factor activity, not to mention the risk of circulatory overload from the volume of the plasma. As a practical matter, the optimum increment of coagulation factor levels that can be achieved by the use of FFP is reached at a dose of ~ 15 mL/kg and results in an increase in coagulation factor levels of 10 to 12%.

The usefulness of FFP as a source of coagulation factors is further limited by the short half-life of clinically important coagulation factors. A common use of FFP is correction of a prolonged prothrombin time due to treatment with warfarin. Warfarin depletes the activity of the vitamin K–dependent coagulation factors II, VII, IX, and X; however, the depletion of factor VII is its most hemostatically relevant effect. The half-life of factor VII is only 5 hours; thus, FFP replacement in this situation is only a temporizing measure until replacement of vitamin K more durably reverses warfarin anticoagulation.

These inadequacies of FFP treatment of coagulopathy were emphasized by the study Abdel-Wahab et al, who analyzed data from 121 patients treated with FFP to correct to an international normalized ratio (INR) of 1.1 to 1.85. Adequate correction of the INR 8 hours after transfusion was achieved in 0.8% of patients, and there was no benefit in reduction in blood loss. These data have particular significance in the preoperative assessment of neurosurgical patients, as the importance of mild prolongation of the INR may not portend an increased risk of hemorrhage. Matevosyan et al assayed coagulation factor levels in 25 neurosurgical patients with INRs of 1.3 to 1.7. They identified hemostatically adequate levels of coagulation factors II, VII, and VIII. The discordance between the INR and the coagulation factor levels may be due to the use of sensitive reagents (principally recombinant tissue factor) in the prothrombin time assay. Based on these finding, the authors recommended against the preoperative use of FFP in patients with slight prolongation of the INR.

**Prothrombin Complex Concentrates**

Concentrates of factors II, VII, IX, and X are prepared by precipitation anion exchange chromatography, and rendered free of infectious agents by solvent detergent treatment or by heating. These complexes may contain variable amounts of the coagulation factor activities and are usually normalized for the activity of factor IX, because their principal use has been for the treatment of hemophilia B. These concentrates have been proposed as treatment for intracerebral hemorrhage secondary to over-anticoagulation with warfarin along with the use of vitamin K. Although several studies indicate that there may be a beneficial effect as measured
by shortening of the prothrombin time and normalization of the INR, it should be noted that not all preparations are identical. Specifically, the majority of the anticoagulant effect of warfarin occurs by its ability to decrease the activity of factor VII. Preparations such as Bebulin (Baxter, Deerfield, IL) have a very low level of factor VII, whereas Octaplex (Octapharma, Hoboken NJ) contains almost as much factor VII as factor IX activity. Consequently, it is important to be aware of the composition of the prothrombin complex concentrates that are available if they are to be used for this off-label indication. As mentioned previously, the half-life of factor VII is very short; thus, repeated doses of prothrombin complex concentrates (PCCs) may be necessary until the effect of vitamin K becomes evident.

Additional concerns regarding the use of PCCs are their potential thrombogenicity. Following their introduction over 40 years ago, multiple reports of local or disseminated thrombosis were associated with these products. It has been appreciated that older manufacturing methods generated activated coagulation factors that were responsible for these occurrences. Contemporary manufacturing techniques, including the use of low levels of heparin, antithrombin, protein C, and protein S in the final product, have reduced this complication of therapy.

Recombinant Factor VII

The thrombogenicity of PCCs, which is ascribed to the presence of activated factor VIIa, has led to their use in the treatment of patients with factor VIII inhibitors. This condition, in which a patient receiving factor VIII replacement for the treatment of hemophilia A develops an antibody that inhibits the activity of factor VIII, makes treatment of bleeding episodes with additional factor VIII impossible. The activated coagulation factors in PCCs, particularly factor VII, are able to bypass the inhibitor and restore hemostasis. Recombinant activated factor VII (rFVIIa) was developed to address the problem of the factor VIII inhibitors and to avoid the thrombogenicity of PCCs and the potential viral contamination of these plasma-derived products. Doses of rFVIIa of 90 µg/kg have been used in patients with these inhibitors with good control of hemorrhagic events. Because this molecule leads to intense activation of the coagulation cascade, it has been proposed as a “broad-spectrum” hemostatic agent that might be used to treat intracerebral hemorrhage, hemorrhage due to warfarin treatment, or postoperative hemorrhage.

Patients with either traumatic or spontaneous intracerebral bleeding have been treated with rFVIIa at doses between 40 and 160 µg/kg. At these doses a reduction in the volume of the intracerebral hematoma was observed, but in most studies there was no impact upon survival or neurologic function at 90 days. Patients receiving this product also had an increased incidence of arterial and venous thromboses. Recombinant factor VIIa has also been evaluated as a treatment of ICH in patients with supratherapeutic anticoagulation with warfarin. Although the INR values were rapidly corrected following treatment, there was no benefit with respect to survival in the patients receiving rFVIIa as opposed to FFP and vitamin K. Consequently, the use of rFVIIa in spontaneous or traumatic ICH is not recommended.

Adverse Reactions to Blood Products

The transfusion of blood products can be associated with adverse events including acute hemolytic transfusion reactions, febrile nonhemolytic transfusion reactions,
TRALI, and delayed hemolytic transfusion reactions. Although the understanding of the pathophysiology of these events has reduced their incidence and provided guidance for further management, these potential complications remind physicians that blood transfusions are not a trivial component of medical and surgical care.

### Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions occur when RBCs are transfused into ABO-incompatible recipients. The immunoglobulin M (IgM) isohemagglutinins, which are present in persons with blood groups A, B, or O, will bind to mismatched RBCs, fix complement, and cause intravascular hemolysis. The hemoglobin liberated by this process will precipitate in the renal tubules and lead to acute tubular necrosis and renal failure. The intravascular release of RBC membrane stroma initiates disseminated intravascular coagulation. The patient usually presents with back pain, hemoglobinuria, fever, and hypotension. Although the severity of these reactions may be mitigated by treatment with intravenous fluids, corticosteroids, and alkaline diuresis, the outcome is often fatal.

A catastrophic acute hemolytic transfusion reaction is almost always due to preventable errors at the bedside, leading to patient misidentification or sample mislabeling. Although clerical or technical errors in the blood bank laboratory can occur, they are seldom the cause. Consequently, institutions need to have processes in place to ensure proper identification of the type and screen specimens entering the blood bank laboratory and the units of blood product leaving the laboratory. These processes include obtaining duplicate type and screen specimens from patients who have not previously been seen at the institution, labeling and signing each type and screen specimen, reviewing the previous transfusion history to identify inconsistencies of ABO and Rh information, and conforming demographic data by two identifiers. Patients who present to the emergency department without identification pose a unique problem in this regard, and institutions should establish a formal plan for this situation to reduce the risk of patient, blood sample, and blood product misidentification.

### Febrile Nonhemolytic Transfusion Reaction

Febrile nonhemolytic transfusion reactions (FNHTRs) are the most commonly encountered adverse transfusion event, and they may occur following the administration of any blood product. These reactions are caused by the release of cytokines from lymphocytes in the donated blood product. Common symptoms include fever, tachycardia, bronchospasm, hypoxemia, and hypotension; rarely they may be fatal. The differential diagnosis of this presentation includes sepsis, pulmonary emboli, myocardial infarction, drug allergy, and TRALI, and these entities should be considered and investigated. These reactions, however, are not associated with hemolysis or liberation of free hemoglobin. The incidence of FNHTR has been reduced by universal leukodepletion by filtration of blood at the time of collection.

Nonhemolytic febrile transfusion reactions can be treated with acetaminophen and antihistamines, or, in more severe situations, with corticosteroids. In addition, premedication with acetaminophen antihistamines may be useful in preventing these events.
Transfusion-Associated Lung Injury

Transfusion-associated lung injury occurs 6 to 8 hours following the administration of blood products (usually FFP or platelets). The patient develops dyspnea and noncardiogenic pulmonary edema, which may be confused with transfusion-associated cardiac overload (TACO), infection, pulmonary embolization, or drug allergy. Histopathological examination of the lungs of patients with TRALI shows aggregates of neutrophils as well as proteinaceous fluid in the alveolar spaces. The neutrophils may be activated by passive transfer of anti–HLA I and II antibodies or antineutrophil antibodies from FFP or from the plasma contained in platelet or RBC transfusions. These antibodies bind to the normal marginated pool of neutrophils that resides in the pulmonary circulation and causes release of the cytokines and lysosomal enzymes. An alternative explanation of this event is that preexisting activation of the neutrophils contained in the pulmonary vessels and activation of the endothelial cells of the pulmonary vasculature by endotoxin or cytokines lead to leukostasis. These events prime the neutrophils for release of their contents upon exposure to the anti-HLA or antineutrophil antibodies. This latter, “two-hit,” model is consistent with the observation that most patients with TRALI are acutely ill prior to the transfusion, and the incidence is higher in patients who have had emergent cardiac surgery or who have received treatment with hematopoietic growth factors (which can also activate neutrophils). The origin of the anti–HLA antibodies and antineutrophil antibodies is important, as they are most likely to be detected in multiparous women. The incidence of anti–HLA antibodies in transfused versus nontransfused men was 1.0% versus 1.7% (no statistically significant difference), whereas the incidence of these antibodies was as high as 32.2% in women with four or more pregnancies. In addition, products derived from donors that have caused one episode of TRALI in one patient are more likely to cause the same problem in subsequent recipients. These observations have led to the elimination of the production of FFP from blood donations from multiparous women, and this strategy appears to reduce the incidence of TRALI. The American Red Cross’s hemovigilance program observed an increase of plasma collection from male donors from 55% in 2006 to 95% in 2008. Over the same interval, the incidence of TRALI associated with the transfusion of plasma as the only blood product decreased from 15.4 events per 10^6 plasma units distributed to 4 events per 10^6 plasma units distributed.

The noncardiogenic pulmonary edema of TRALI is treated with mechanical ventilation employing low tidal volumes, diuretics, and intravenous corticosteroids, although the value of the latter has been questioned. The person whose blood donation was associated with TRALI should be screened for anti–HLA and antineutrophil antibodies, and the affected patient should not receive products from this particular donor.

Delayed Hemolytic Transfusion Reactions

Patients who have been multiply transfused or have been pregnant may develop alloantibodies against the “minor” blood group antigen such as Kell, Kidd, Duffy, or Lutheran. These antibodies fall to undetectable levels over months or years, so that they may not be identified by the routine antibody screen prior to transfusion of subsequent units of blood. Should the newly transfused RBCs contain one (or more) of these antigens, they will generate an anamnestic response producing alloantibodies that will bind to the transfused RBCs. The patient will present with a sub-
acute decrease of hemoglobin concentration, which may be mistaken for occult hemorrhage. Laboratory evaluation will show a slight rise of indirect bilirubin, a decrease of haptoglobin, and a positive direct antiglobulin test. Often the anemia is mild, and additional blood transfusions are not necessary; however, should patients need additional units of RBCs, they will need to be negative for the mismatched minor blood group antigen.

Conclusion

The availability of blood components has enabled surgeons to support patients during operative procedures and has facilitated good clinical outcomes of life-threatening conditions. The appropriate use of blood products requires an understanding of their sources, their limitations, and their potential toxicities. This knowledge needs to be combined with the best available clinical evidence to optimize the benefit and reduce the risk of treatment with blood products.

KEY POINTS

- Blood product replacement needs to be guided by the clinical situation and not by adhering to arbitrary criteria of hemoglobin, platelet count, or coagulation parameters.
- Mild abnormalities of the INR (< 1.7) are usually not associated with clinically significant depletion of coagulation factors. Factor replacement therapy is usually not necessary.
- No significant advantages have been identified for directed donor blood products.
- Rigorous attention to patient identification and specimen labeling is essential for the safe administration of blood products.

REVIEW QUESTIONS

1. True or false?
   A. Red blood cells stored in standard fashion are suitable for transfusion for up to 12 weeks.
   B. Red blood cells stored in standard fashion are suitable for transfusion for up to 6 weeks.
   C. One unit of packed RBCs contains a volume of 225 cc.
   D. One unit of packed RBCs should raise a recipient's hemoglobin 2 g/dL and their hematocrit 0.06.
   E. Blood is filtered at the site of collection to reduce white cell contamination of blood products.

2. True or false?
   A. Patients with platelet counts = 100,000/µL are always safe for surgery.
   B. Patients with platelet counts < 100,000/µL always require platelet transfusion.
   C. One unit of platelets transfused will typically raise the platelet count by 40,000 to 60,000/µL.
D. The platelet count should be maintained at > 100,000/µL for at least 48 to 72 hours following a neurosurgical procedure.

E. The platelet count should be maintained at > 50,000/µL for at least 7 days following a neurosurgical procedure.

3. True or false?
   A. Autologous blood transfusions entail the patient’s donating one to two units of whole blood before a surgical procedure.
   B. Directed donor blood transfusions entail a first-degree relative of the patient donating one to two units of whole blood before a surgical procedure.
   C. Autologous blood units must be strictly quarantined from the remainder of the blood supply.
   D. Directed donor blood transfusions have a lower rate of transfusion-associated disease (e.g., HIV, hepatitis B or hepatitis C).
   E. Directed donor blood from a relative carries an increased risk of graft-versus-host disease and requires pretransfusion gamma irradiation of the blood.

4. According to Carson et al.’s 2002 manuscript regarding postoperative hemoglobin and mortality, are these statements true or false?
   A. The 30-day mortality was 0% if the patient’s postoperative hemoglobin was 7.1 to 8.0 g/dL.
   B. The 30-day mortality was 5% if the patient’s postoperative hemoglobin was 7.1 to 8.0 g/dL.
   C. The 30-day mortality rate was 16% if the patient’s postoperative hemoglobin was 3.1 to 5.0 g/dL.
   D. The 30-day mortality rate was 30% if the patient’s postoperative hemoglobin was 3.1 to 5.0 g/dL.
   E. The 30-day mortality rate was 64% if the patient’s postoperative hemoglobin was less than 3.0 g/dL.

5. Potential blood conservation strategies for patients who are members of Jehovah’s Witnesses may include:
   A. Autologous blood transfusion
   B. Preoperative erythropoietin
   C. Cell savers with a closed blood circuit
   D. Normovolemic hemodilution
   E. All of the above

6. True or false?
   A. Prothrombin complex concentrate (PCC) preparations contain factors II, VII, IX, and X.
   B. Prothrombin complex concentrate preparations from different manufacturers have similar concentrations of factors.
   C. Prothrombin complex concentrate preparations are normalized for the activity of factor VII.
   D. The half-life of factor VII is long enough so that repeated doses of PCCs is typically not required after vitamin K has been administered.
   E. Local or disseminated thrombosis is a potential risk associated with use of PCCs.
References


IV
Management of Venous Thrombosis in Neurosurgical Conditions
Venous Thromboembolism (DVT and PE): Diagnosis and Treatment
Graham F. Pineo and Mark G. Hamilton

Definition
Deep vein thrombosis (DVT) most commonly involves the deep veins in the lower extremities. Thrombosis confined to the calf veins or distal DVT usually remains confined to the deep veins distal to the popliteal vein and has no serious consequences. However, approximately 20% extend into the popliteal vein and become proximal. Proximal vein thrombosis involves the popliteal, femoral, and iliac veins and is the most common source of pulmonary embolism (PE). Less commonly, the deep veins in the upper extremity may become thrombosed particularly in patients with indwelling vascular devices. Thrombosis may occur in more unusual locations, such as the cerebral venous sinus or the venous system in the splanchnic bed. Superficial venous thrombosis, commonly referred to as thrombophlebitis, is a relatively benign disorder except where the thrombus may extend into the deep venous system in the groin or at the level of the knee.

Pulmonary embolism most commonly originates in the deep venous system of the legs. Other less common sources include the deep pelvic veins; the renal veins or inferior vena cava; the right side of the heart, particularly in patients with cardiomyopathy or ischemic heart disease; and rarely from the axillary veins. Up to 70% of patients with PEs have evidence of DVT, and more than 50% of patients presenting with a proximal DVT already have PE. DVT and PE are referred to collectively as venous thromboembolism (VTE).

Incidence
The incidence of VTE is difficult to ascertain, as many patients are asymptomatic. This is particularly true in patients in the postoperative period or in other hospitalized patients, because as many as 50% of these cases of VTE may be silent. The increasing use of more sensitive multidetector computed tomography (CT) scanners has markedly increased the incidence of PE, many of which cases are asymptomatic or incidental, and as the scanners have become more sensitive, more subsegmental PEs are being reported. However, there has been no change in the number of central or fatal PEs over this same time period. The management of these unexpected PEs is still controversial and, except for the small subsegmental emboli, anticoagulant treatment is recommended.

The annual incidence of VTE is estimated to be approximately 117 cases per 100,000 persons. Estimates in the United States place the incidence of VTE somewhere between 350,000 and 600,000 cases per year. Hospital discharge data in the United States for the year 2003 show that there were over 38,000,000 hospital
Manag ement of Venous Thrombosis

Discharges, with 12,000,000 of these patients on both medical and surgical wards being at risk for VTE based on the American College of Chest Physicians (ACCP) guidelines.14

Effective prophylaxis against VTE is now available for most high-risk patients (see also Chapter 11).15 Most fatal PEs occur suddenly and without warning, demonstrating the importance of prevention as the most critical step for reducing death from PE. Furthermore, the prevention of death and morbidity from VTE is more cost-effective than treating the established disease.16 Numerous national and international guidelines are available for the prevention of VTE such as those produced regularly by the ACCP.15

Serious Consequences of Venous Thromboembolism

Fatal Pulmonary Embolism

Clearly the most feared complication in patients with VTE is fatal PE.17–19 Patients with massive PE have an increase in pulmonary vascular resistance from the thrombus obstruction as well as pulmonary vascular constriction.18 This leads to increased pressure in the right side of the heart and septal shift toward the left ventricle, which leads to arterial hypotension, cardiogenic shock, and cardiac arrest unless the obstruction can be lessened by thrombolysis or by mechanical means. The spectrum of PE ranges from asymptomatic patients with incidental PE to patients with submassive PE who may have hypotension and right ventricular dysfunction but who will survive if further embolism can be prevented with anticoagulation.18,19 Also many patients with PE have evidence of repeat small embolism prior to the larger pulmonary embolus, which leads to the diagnosis.18 Rarely, patients who have DVT and a patent foramen ovale may develop paradoxical embolism of thrombotic material leading to stroke.20,21

Postthrombotic Syndrome

The postthrombotic syndrome (PTS) results from venous valve dysfunction with or without persistent proximal vein obstruction leading to venous hypertension. This can result in the redirection of blood flow from the deep venous system to the superficial veins with increased edema, impaired circulation, and ultimately venous ulceration.22,23 The PTS, therefore, presents as a spectrum that includes lower extremity edema that is worse by the end of the day, redness and hyperpigmentation, and venous ulceration. PTS develops in up to 30% of patients after an initial episode of proximal DVT.22,23 The development of recurrent iliofemoral thrombosis in the same leg increases the risk of developing PTS, as does inadequate anticoagulation early in the treatment.24,25 The use of graduated compression stockings has been shown to significantly decrease the incidence of PTS, particularly the more severe forms, if the stockings are applied shortly after the development of proximal DVT and are used consistently for up to 2 years.26,27

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (CTPH) may develop in 0.5 to 1.5% of patients presenting with an initial PE, with some estimates being even
Etiology and Pathogenesis

Venous thrombi are composed mainly of fibrin and red blood cells with variable numbers of leukocytes and platelets. Thrombosis usually begins in the valve pockets in the distal veins and propagate proximally. The thrombogenic stimuli as identified by Virchow still apply: stasis of blood, activation of blood coagulation, and damage to vessel walls. The protective mechanisms include lysis by fibrinolytic enzymes derived from plasma and endothelial cells, clearance of activated coagulation factors by mononuclear phagocytes in the liver, and inactivation of activated coagulation factors by circulating inhibitors such as antithrombin and activated protein C.

Risk Factors for Venous Thromboembolism

Several acquired and inherited risk factors for VTE have been identified. Patients who develop VTE at a younger age, multiple family members with VTE, idiopathic VTE, recurring VTE, or a history of multiple spontaneous abortions should be evaluated for acquired or inherited coagulopathies, the so-called thrombophilias. The most common of these are factor V Leiden, the prothrombin mutant, and the acquired antiphospholipid antibody syndrome. Patients with antithrombin deficiency or those with multiple forms of thrombophilia are at highest risk for thrombosis. The use of oral contraceptive pills or pregnancy may be the first indication of a predisposition for thrombosis in patients with thrombophilia.

Patients with idiopathic or unprovoked VTE or with ongoing risk factors such as cancer or prolonged immobility are at the greatest risk for recurrent VTE. Various strategies for risk assessment for recurrent VTE incorporating D-dimer testing have been developed (e.g., REVERSE Study or DASH), which include factors such as PTS, age, sex, obesity, and the sex hormone–associated VTE. These factors have been shown to have predictive value for recurrent VTE, but have not as yet become part of clinical practice.

Risk factors for upper extremity DVT include younger age, male sex, smoking, and indwelling intravascular devices. Indeed, indwelling intravascular devices account for 80% of upper extremity DVT.

Risk Factors for Venous Thromboembolism in Neurosurgery Patients

Brain Tumors

Patients with brain tumors are at high risk for VTE. Risk factors include malignant tumor, advanced age, longer duration of surgery, and paresis. In one study, the risk of clinically diagnosed VTE within 30 days of craniotomy was 3.9% for all
Spinal Surgery
The overall risk of VTE following spinal surgery is relatively low, but higher risk factors include a combined anterior-posterior approach, multiple operative levels, and patient-related factors such as older age, prior VTE, and malignancy. A population-based retrospective analysis of discharges from California hospitals found the risk of symptomatic VTE within 90 days of surgery to be 0.5% among patients who underwent spinal surgery for a nonmalignant disease, whereas the risk of VTE was 2.0% for patients who had spinal surgery for malignant disease. The ACCP classifies spinal surgery as low risk for most patients with nonmalignant disease and moderate for patients with malignancy.

Trauma Patients with Spinal Cord Injury
Trauma patients pose a high risk for VTE, with risk factors including traumatic inflammation, fractures, immobilization, and surgical intervention. At the same time, multiply injured patients with visceral spinal and head injury also pose a high risk for bleeding. The risk is highest among patients with spinal trauma, acute spinal cord injury, or traumatic brain injury. The baseline risk for VTE in patients with major trauma has been estimated to be at least 3.5%, with higher risk (8–10%) in patients with traumatic brain or spinal cord injury.

Intracranial Hemorrhage
Patients with intracranial or subarachnoid hemorrhage are at significant risks for the development of VTE. In one series, the incidence of VTE was 7.2%, with the incidence of a symptomatic DVT detected by ultrasonography being as high as 24% in patients with subarachnoid hemorrhage. Patients with acute intracranial hemorrhage with severe neurologic deficit and a high D-dimer are at increased risk for developing DVT. In one meta-analysis, the use of heparins or a heparinoid decreased the incidence of DVT and PE, with a nonsignificant reduction in mortality and a nonsignificant increase in hematoma enlargement in patients with hemorrhagic stroke when compared with placebo or mechanical methods.

Stroke Patients
Patients with acute stroke (ischemic or hemorrhagic), particularly with limb paralysis, are at high risk for VTE. Risk factors peculiar to stroke patients include reduced mobility, elderly age, and multiple comorbid disorders such as heart or respiratory failure, previous myocardial infarction or ischemic stroke, as well as the severity of the stroke as indicated by the National Institutes of Health (NIH) Stroke Scale score.

In all of these disorders, the risk of intracranial or intraspinal spinal bleeding must be weighed against the risk of fatal PE. Modalities shown to be useful in the
prevention of VTE in neurosurgical patients include low molecular weight heparin (LMWH), intermittent compression devices, and, in some cases, the use of an inferior vena caval filter.

**Venous Thromboembolism and Pregnancy**

Pregnancy poses a risk for VTE particularly in patients with thrombophilia. The highest-risk thrombophilias include antithrombin deficiency, protein C or S deficiency, homozygosity for the factor V Leiden mutation or antiphospholipid antibody (APLA), and combined defects. Other risk factors include prior VTE, multiple birth pregnancies, older age, and cesarean section. VTE can occur in any of the three trimesters, but it is highest in the postpartum period, particularly following cesarean section. Venous compression of the left external iliac vein by the iliac artery adds a further risk for thrombosis. In the more extreme form, called the May-Thurner syndrome, thrombosis is a known complication at anytime, but the risk is increased in pregnancy. Prevention or treatment of VTE in pregnancy requires the use of subcutaneous LMWH throughout pregnancy because of the teratogenic potential of warfarin. Warfarin can be safely used in the postpartum period.

**Diagnosis of Venous Thromboembolism**

The clinical diagnosis of DVT is quite nonspecific because the same symptoms and signs can be caused by other disorders. The usual clinical features of DVT include unilateral calf or leg pain, tenderness and swelling, and occasionally discoloration with venous distention of superficial veins and, in more extreme cases, discoloration including cyanosis. The clinical features may not predict the extent of thrombosis, in that some patients with more florid leg signs and symptoms have minimal disease on objective testing, whereas other patients who have extensive venous thrombosis may show few or no clinical signs whatsoever. For that reason, objective testing is required on all patients to confirm the diagnosis.

**Pretest Probability Assessment of Deep Vein Thrombosis**

Based on prospective studies, pretest probability (PTP) formulas have been developed for the diagnosis of DVT. The most commonly used is the Wells rule (Fig. 10.1). Patients with a score of 2 or less can be categorized as “DVT unlikely,” whereas those with a score of greater than 2 are “DVT likely.” Based on the original studies and systematic reviews, the prospective diagnosis of DVT can be shown to be of low, moderate, or high probability, or “DVT unlikely” or “DVT likely” based on the results of ultrasound testing. The results of PTP along with the measurement of the D-dimer can be integrated into diagnostic strategies for the diagnostic management of DVT. The clinical signs and symptoms of PE are also highly nonspecific, and, as with DVT, the diagnosis must be confirmed by objective testing. Common symptoms include transient dyspnea and tachypnea, chest tightness or pleuritic pain, and cough (rarely with hemoptysis). In patients with submassive PE, dyspnea and tachypnea may become severe, with right-sided heart failure and cardiovascular collapse with syncope, hypotension, and coma, and in such cases the outcome is frequently fatal. In fact, patients who die of massive PE usually do so within
Suspected DVT

Fig. 10.1 Diagnostic management of suspected deep vein thrombosis (DVT). U/S, ultrasound. (Adapted from Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. J Thromb Haemost 2013;11:412–422. Reprinted with permission.)

the first 30 to 60 minutes after the onset, when treatment might not have been initiated. For that reason prophylaxis of PE is of upmost importance.18

Pretest probability Assessment of Pulmonary Embolism

As with DVT, there are predictive rules for the diagnosis of PE, which can be confirmed by either CT scanning or ventilation/perfusion (VQ) scanning.82–85 The two clinical decision rules in widespread use are the Wells score82,83 and the Geneva score (Fig. 10.2).84,85 Based on PTP, patients with a score of 4 or less can be categorized as “PE unlikely,” whereas those with a score of more than 4 are “PE likely.”82–85 Prospective management studies have confirmed that patient risk for PE can be accurately divided into low, moderate, or high, or as “PE likely” or “PE unlikely.” The assessment of PTP combined with the D-dimer assessment can be used to streamline the diagnostic approach to the patient with PE.

D-Dimer Assay

The D-dimer assay is the most useful test in excluding the diagnosis of VTE.86–89 A quantitative D-dimer assay with a rapid turnaround time has been most useful using either an enzyme-linked immunosorbent assay (ELISA) or latex agglutination. The D-dimer test cannot be used to support the diagnosis of VTE because numerous other abnormalities produce positive D-dimer, such as cancer, infection,
Suspected PE (Using CTA)

[Diagram of Suspected PE Clinical Probability Assessment]

Fig. 10.2 Diagnostic management of Suspected pulmonary embolism (PE). CTA, computed tomography angiography; U/S, ultrasound. (Adapted from Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. J Thromb Haemost 2013;11:412–422. Reprinted with permission.)

pregnancy, trauma, surgery, sepsis, and advancing age. For that reason the D-dimer assay is most useful in streamlining the diagnosis of VTE in outpatients, as most in-hospital patients have a positive D-dimer. The D-dimer assay is used in conjunction with PTP assessment. Patients with a low PTP and a negative D-dimer may not require further investigations.

Other Laboratory Tests

Measurement of troponin and brain natriuretic peptide (BNP) provides evidence of myocardial dysfunction associated with PE, and can be useful in determining whether or not patients with PE require thrombolysis or mechanical relief of the vascular obstruction.

Objective Testing for Deep Vein Thrombosis

The diagnostic test most commonly used for the diagnosis or exclusion of DVT is ultrasonography; less commonly used nowadays is venography. Both of these tests have been validated by prospective management studies, which have demonstrated the safety of withholding anticoagulant therapy in patients with negative test results.

Ultrasonography is noninvasive and can easily be repeated serially if necessary. It is readily available and can be done at the bedside. Noncompressibility of a vein
Management of Venous Thrombosis

Segment is the most important component of the study, but color flow and venous augmentation can be added. Ultrasound has a high sensitivity and specificity for symptomatic proximal DVT but less for distal DVT (65%), so that repeat examinations are needed to detect propagation into the proximal veins if anticoagulation treatment is not started. Ultrasound has limited value in diagnosing pelvic DVT.32,78

The diagnosis of recurrent DVT is problematic unless a new segment of vein is involved or there is extension of a previous thrombus.39,94–98 Also, ultrasonography may remain abnormal in 30% of patients even at 1 year after an initial event. Measurement of D-dimer may be of value if it is negative, but this requires further study.96,97 Ascending venography may be useful in diagnosing recurrent DVT or in patients in whom repeat ultrasonography is inconclusive or repeat testing is impractical.98

Patients with a low PTP and a negative D-dimer may require no further testing, whereas those with a positive D-dimer require objective tests with ultrasonography. Patients with a high PTP do not undergo D-dimer testing and proceed directly to ultrasonography. If ultrasonography is negative, the patient may require repeat testing or in some cases venography (Fig. 10.1).13,32,77,78,97

Computed tomography venography94 and venography by magnetic resonance imaging (MRI)99 have been useful in demonstrating proximal DVT in conjunction with the diagnosis of PE. MRI of the pelvic veins can be useful, for example, in pregnancy or in patients with isolated iliac vein thrombosis.

Objective Testing for Pulmonary Embolism

Computed Tomography Angiography

Computed tomography angiography (CTA) is the diagnostic test of choice for the diagnosis of PE.6,100,101 It is widely available, and has been shown to have a sensitivity of 82 to 100% and specificity of 89 to 98%.100 The sensitivity can be further improved by simultaneously performing CT venography of the lower extremities.100 The technology for CTA has rapidly evolved from single detectors to multiple detectors (64 to 256 rows). Multiple-detector CTA has a higher sensitivity for PE by enabling better visualization of peripheral vessels when compared with single-detector CTA, leading to a higher rate of detection of subsegmental PE.11 As mentioned earlier, the management of these small PE remains controversial and in some cases anticoagulants can be safely withheld.11

Computed tomography angiography has been integrated into the diagnostic strategy for the diagnosis of suspected PE (Fig. 10.2). Some patients with a low PTP and a negative D-dimer may need no further testing, whereas those who have a positive D-dimer require objective testing with CTA. Patients with a high PTP go directly to CTA testing. If the CTA is nondiagnostic, further testing is required with ultrasonography of the legs or in some cases of pulmonary angiography.32,102

Ventilation/Perfusion Lung Scanning

Ventilation/perfusion (VQ) lung scanning compares ventilation and perfusion as part of the evaluation for PE.103–106 Perfusion is assessed by injection of isotopically labeled microaggregates of human albumin, and ventilation is assessed by inhaling radioactive aerosol. A mismatch of ventilation and perfusion is considered a high probability for PE. A negative VQ scan is adequate to eliminate the diagnosis of PE. However, more than 70% of patients have a nondiagnostic VQ scan and require further testing, usually by ultrasonography of the legs or performance of CTA.
An integrated approach to the diagnosis of suspected PE using VQ scanning is also established. Patients with a low PTP and a negative D-dimer may require no further testing, whereas those with a positive D-dimer have testing with a VQ scan. Those with a high PTP go directly to VQ scanning. If it is nondiagnostic, they will require ultrasonography of the legs, CTA, or, in some cases, pulmonary angiography. VQ scanning is still useful for patients who have anaphylaxis to intravenous contrast media or significant renal impairment or in young women of child-bearing age to eliminate the high radiation exposure to the breasts provided by CTA.

**Magnetic Resonance Imaging**

Another diagnostic test for evaluation of PE is MRI angiography. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED-III) study, MRI was technically inadequate in 25% of patients despite the fact that all centers were experienced with this technique. Technically adequate MRI had the sensitivity of 78% and the specificity of 99%. With the addition of MRI venography, sensitivity improved to 92% with specificity of 96%, but 52% of patients had technically inadequate results. It was hoped that magnetic resonance angiography (MRA), which has no ionizing radiation exposure, would be a useful diagnostic test in pregnant patients. Although MRI appears to be safe during pregnancy, there have been conflicting data about the safety of gadolinium and fetal development. Also, gadolinium in the presence of renal insufficiency can lead to nephrogenic systemic fibrosis. This can cause a progressive thickening and hardening of the skin and other body tissues, including the gastrointestinal tract and the peripheral joints. Therefore, the hope that MRI would be useful in the diagnosis of PE in patients with renal insufficiency where contrast enhanced CTA is contraindicated has not been realized.

**Pulmonary Angiography**

Pulmonary angiography using selective catheterization of pulmonary arteries is relatively safe in experienced hands and can be used when other approaches are inconclusive or when definitive knowledge about the presence or absence of PE is required urgently, as in patients in the intensive care unit.

**Echocardiography and Biomarkers**

Although echocardiography is not sensitive for the diagnosis of PE, it can be useful in evaluating the evidence of right ventricular dysfunction in the setting of PE. Findings on transthoracic echocardiography that suggest right ventricular dysfunction include right ventricular dilatation, hypokinesis, paradoxical intraventricular septal wall motion, tricuspid regurgitation, and pulmonary hypertension. Elevated troponin or BNP results provide further evidence of significant cardiac damage in the presence of PE and can be helpful in assessing patients who may require thrombolysis.

**Treatment of Venous Thromboembolism**

The objectives of treatment of the patients with VTE are to prevent death from PE, to prevent recurrent VTE, and to prevent the postthrombotic syndrome. Initial
anticoagulant treatment of VTE consists of either LMWH or unfractionated heparin given intravenously or by subcutaneous injection for a period of 4 to 5 days in conjunction with an oral anticoagulant that is normally a vitamin K antagonist (VKA), such as warfarin or acenocoumarol, started in conjunction with the heparins. These are continued until the international normalized ratio (INR) is therapeutic on two consecutive days. The new oral anticoagulants offer convenient options for both the initial and long-term treatment of VTE.

Heparin Therapy

Low Molecular Weight Heparin as the Initial Treatment

The LMWHs are derivatives of commercial heparin, with a mean molecular weight of 4 to 5 kd. The LMWHs differ from regular-weight heparin in numerous ways. Of particular importance are the following: they have increased bioavailability (i.e., > 90% after subcutaneous injection), they have a prolonged half-life, and they have a predictable clearance enabling a once or twice daily injection. Furthermore, there is a predictable antithrombotic response based on body weight, so that treatment can be provided without laboratory monitoring.

The LMWHs that are given by subcutaneous injection have been compared with continuous intravenous unfractionated heparin (UFH) in numerous clinical trials for the treatment of proximal DVT and PE, with long-term follow-up to assess outcome measures. Systematic reviews of these studies indicate that LMWH is as effective as UFH with a reduction in major bleeding and mortality. Studies in which LMWH has been used on an outpatient basis have also shown these agents to be effective and safe when compared with intravenous UFH given on an inpatient basis. LMWH has been shown to be cost-effective for the treatment of VTE when compared with intravenous UFH. LMWH is recommended as the anticoagulant for the initial treatment of VTE by the ACCP.

Long-Term Low Molecular Weight Heparin Treatment

Long-term treatment of acute VTE with LMWH has been evaluated in several randomized clinical trials in comparison with oral anticoagulant treatment. In the two studies in patients with cancer and thrombosis, long-term LMWH for 3 or 6 months was more effective than warfarin in the prevention of recurrent VTE, and in one study there were fewer bleeding complications. In clinical practice guidelines, LMWH is suggested over warfarin for the treatment of thrombosis associated with cancer for the first 3 to 6 months of long-term treatment.

Unfractionated Heparin Treatment

The anticoagulant activity of UFH depends on a unique pentasaccharide that binds to antithrombin markedly enhancing the inhibition of thrombin and activated factor X (Xa). Only about one third of the heparin molecules contain the unique pentasaccharide sequence that potentiates the activity of endogenous antithrombin. Heparin also catalyzes the inactivation of thrombin by heparin cofactor 2, which acts independently of antithrombin.
The anticoagulant response to UFH varies widely among patients so that it is necessary to monitor the anticoagulant effect either by use of the activated partial thromboplastin time (aPTT) or by heparin levels, and to titrate the UFH dose accordingly. The use of a prescriptive approach such as the weight-based nomogram achieves adequate anticoagulation within the first 24 hours of treatment and results in a reduced rate of recurrent VTE.124–127

The simultaneous use of intravenous or subcutaneous UFH or subcutaneous LMWH with VKA therapy has become standard practice for the initial management of most patients with VTE.122,126,127 Exceptions include patients who are unstable and may require immediate medical or surgical intervention, such as thrombolysis or insertion of a vena caval filter; patients who are at high risk of serious bleeding; and patients who have severe renal insufficiency. Adjusted-dose UFH by subcutaneous injection has been used for the initial treatment of VTE with an efficacy and safety similar to fixed-dose LMWH but is more cumbersome and requires monitoring with the aPTT.128 The LMWH or UFH is continued until the INR is at the therapeutic level for two consecutive days.

The main adverse effects of the heparins are bleeding, thrombocytopenia, and osteoporosis. Patients at particular risk of bleeding include those who have had recent trauma or surgery, and those who have other clinical disorders that predispose them to bleeding, such as peptic ulcer, cancer, liver disease, or hemostatic defects.117 When patients experience bleeding on heparin therapy, their management depends on the location and severity of bleeding, the level of the aPTT, and their risk of recurrent VTE. The heparin infusion should be discontinued temporarily or permanently, and in urgent situations protamine sulfate may be administered. Those patients at risk of recurrent VTE may be candidates for insertion of a temporary or permanent vena caval filter.114

Heparin-induced thrombocytopenia (HIT) is a well-recognized complication of UFH therapy; it is much less common with the use of LMWH. It usually occurs in the first 4 to 10 days after commencing therapy.129 About 1 to 2% of patients receiving UFH will experience a fall in platelet count to less than the normal range or a 50% drop in the platelet count within the normal range. In most of these patients, the thrombocytopenia is mild to moderate and of no clinical significance. It is considered to be a direct effect of the heparin.129–131 However, approximately 0.1 to 0.2% of patients receiving UFH by any route develop an immune thrombocytopenia mediated by an immunoglobulin G (IgG) antibody to a complex of PF4 and heparin. The development of HIT may be accompanied by arterial or venous thrombosis, which can lead to serious consequences including amputation or death. It has been shown that the incidence and severity of HIT varies among different patient populations, being more prevalent in patients having cardiac or orthopedic procedures than in medical patient.131

To aid in the clinical diagnosis of HIT, a formula that assesses the 4 T’s is used,132–134 the 4 T’s being treatment with heparin, timing of the initial dose, the degree of thrombocytopenia, and other factors that can be seen in patients with HIT. When the clinical diagnosis of HIT is made, heparin in all forms must be stopped immediately. In most centers a screening test, which is an ELISA for the heparin-platelet factor 4 complex, can be measured. Because there are frequent false-positive test results with the ELISA test, a confirmatory test should be performed if available, and the most accurate of these tests is the serotonin release assay. Both of these tests require lengthy times before the results are available, so that management must be instituted on clinical grounds. For patients requiring ongoing anticoagulation, there are several choices, including the use of a specific antithrombin
agent, argatroban, or the direct thrombin inhibitor lepirudin. More recently, fondaparinux has been shown to be useful for the treatment of HIT.

Osteoporosis can occur in patients on UFH, particularly those taking it for 6 months or more and those who receive therapeutic doses. Bone demineralization can lead to vertebral fractures or fractures of long bones, and this defect may not be reversible. Osteoporosis has not been seen with the long-term use of LMWH.

Fondaparinux

Fondaparinux is a synthetic inhibitor of factor Xa that markedly increases the activity of antithrombin and therefore differs from LMWH. It is rapidly absorbed following subcutaneous injection and has an elimination half-life of 17 to 21 hours in healthy subjects and is prolonged in patients over the age of 75. About 77% of the drug is excreted unchanged in the urine, and drug levels increase with decreasing renal impairment. Therefore, fondaparinux is contraindicated in patients with severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min) and should be used with caution in patients with mild to moderate renal failure. Fondaparinux has been approved as a substitute for unfractionated heparin or LMWH for the initial treatment of VTE. However, fondaparinux has not replaced LMWH for the initial treatment of VTE in most countries mainly because of the prolonged half-life, the concern about using it in patients with renal insufficiency, and the fact that the anticoagulant effect cannot be blocked.

Long-Term Treatment with Vitamin K Antagonist—Warfarin

The anticoagulant effect of warfarin is mediated by the inhibition of vitamin K–dependent gamma-carboxylation of coagulation factors II, VII, IX, and X, and warfarin treatment results in the synthesis of immunologically detectable but biologically inactive forms of these coagulation proteins. Warfarin also inhibits the biological activity of proteins C and S, which are responsible for the inhibition of the coagulation process by activated protein C. Because the activity of proteins C and S are inhibited before there is adequate anticoagulant effect on the other clotting factors, it is mandatory to inhibit the coagulation system with an agent such as LMWH or fondaparinux for a period of time until there is adequate suppression of all the vitamin K–dependent factors. As the dose–response relationship varies widely among patients, the dose must be monitored with the use of a laboratory test—the INR. The range of the INR for the treatment of VTE is 2 to 3. There is a relatively good relationship between recurrent thrombosis when the INR is in the subtherapeutic range and spontaneous bleeding when the INR becomes significantly elevated. Numerous drugs may interfere with warfarin therapy, but a critical appraisal of the literature indicates that such interactions tend to be poorly supported by evidence in most cases. There are several genetic polymorphisms that may make patients more or less sensitive to warfarin such as CVP2C9, CVP4F2, or VKORC1.

More frequent determinations of INR are required with the initial use of warfarin, but once the anticoagulant effect is stable INR may be measured in 2 to 4 weeks, and many patients do not require many dose adjustments. There are warfarin nomograms and computer software programs that assist caregivers in the
control of warfarin therapy.\textsuperscript{115} Also, the use of self-testing with portable INR monitors can simplify management of warfarin, and in many cases patients can self-manage their warfarin therapy. Anticoagulant management clinics have also improved the quality of warfarin treatment.\textsuperscript{112}

**Duration of Anticoagulant Therapy and Recurrent Venous Thromboembolism**

The appropriate duration of anticoagulant treatment for VTE has been evaluated in numerous trials.\textsuperscript{111,146–150} These trials have demonstrated that warfarin therapy is highly effective in preventing recurrent VTE, but there is an increase in the risk of bleeding.\textsuperscript{146–150} The current approach to the treatment of VTE is to continue oral anticoagulant therapy for a full 3 months to suppress the coagulation system. This is referred to as initial treatment, and anything beyond this is referred to as extended treatment.\textsuperscript{111,151} Patients who require anticoagulation therapy beyond the extended period are in long-term treatment.\textsuperscript{111,151}

Patients who have VTE secondary to a precipitating event such as surgery or trauma have a lower incidence of recurrent VTE, and the usual treatment period of anticoagulation is only 3 months.\textsuperscript{111} Patients with the first episode of unprovoked or idiopathic VTE should be treated for at least 3 months. For those patients at high risk of bleeding, 3 months may be the duration of anticoagulant therapy. However, in most patients, the treatment period is extended for 6 to 12 months.\textsuperscript{111} The decision regarding extended and long-term treatment must be individualized, taking into consideration the estimated risk of recurrent VTE and the risk of bleeding as well as patient compliance and preference. In all cases the anticoagulant management program must be reviewed periodically with respect to risk benefit assessment.\textsuperscript{111}

Patients who have a second episode of unprovoked VTE usually require indefinite anticoagulation unless the bleeding risk is high, but in all cases the treatment program should be reviewed periodically.\textsuperscript{111}

**Adverse Effects of Oral Anticoagulants**

Bleeding is the major side effect of oral anticoagulant therapy.\textsuperscript{111,152–154} The most important factor leading to the bleeding risk is the intensity of the INR, with clinically important bleeding being higher when the targeted INR increases above 4.5. Other factors include a history of bleeding, previous stroke or myocardial infarction, hypertension, renal failure, and diabetes.\textsuperscript{151} There is a strong negative relationship between the percentage of time that patients are within the targeted INR range and both bleeding and a recurrent thrombosis.\textsuperscript{154} Oral anticoagulant therapy in the elderly presents further tendencies to increased bleeding, as do the presence of cancer, intestinal polyps, and renal failure.\textsuperscript{155}

**Management of Over-Anticoagulation**

Bleeding in patients on VKA therapy with an elevated INR must be evaluated for the degree of elevation of the INR and the clinical circumstances.\textsuperscript{112,156} The options available include temporary interruption of the warfarin treatment, or the admin-
istration of vitamin K or of blood products such as fresh frozen plasma or prothrombin complex concentrates. If the INR is mildly increased and the patient is not bleeding, no specific therapy is necessary other than reducing the warfarin dose. With a more marked increase of the INR in patients who are not bleeding, treatment with small doses of vitamin K (e.g., 1 mg per day) given either orally or subcutaneously should be considered. With more marked increase in the INR, particularly in patients who are actively bleeding, the coagulation defect should be corrected. Vitamin K can be given intravenously or subcutaneously. If the bleeding defect requires further correction, fresh frozen plasma may be given, or, if anticoagulation should be more rapidly reversed, prothrombin complex concentrates can be given intravenously. If prothrombin complex concentrates are not readily available, recombinant activated factor VII has been used to control life-threatening bleeding.

Management of Patients on Long-Term Oral Anticoagulant Therapy Who Require Surgical Intervention

Patients on long-term anticoagulation frequently require temporary interruption of treatment for surgery or other invasive procedures. The risk of recurrent VTE when anticoagulants have been discontinued must be weighed against the risk of bleeding if either UFH or LMWH is administered before or after the surgical procedure or if oral anticoagulant therapy is continued at therapeutic levels. The approach chosen will depend on the risk benefit assessment of each individual patient. Options include continuing warfarin at therapeutic doses for procedures such as most dental extractions, skin biopsies, or ophthalmologic procedures; lowering the warfarin dose to maintain an INR in the lower or subtherapeutic range during the surgical procedure; and discontinuing warfarin for 3 to 5 days before the procedure to allow the INR to return to normal, with or without bridging with LMWH at prophylactic or therapeutic doses before the procedure and then after the procedure until warfarin therapy is therapeutic.

New Oral Anticoagulants

Recently, there has been much interest in the development of new antithrombotic agents that may be able to replace warfarin. The most advanced agents are specific inhibitors of activated factor X (Xa) or thrombin (IIa). These agents have the advantage that they can be given by the oral route once or twice daily, they require no laboratory monitoring, and, in most cases, the same dose is taken by all patients. The agents available at present are either factor Xa inhibitors: rivaroxaban (Xarelto; Bayer, Johnson & Johnson), apixaban (Eliquis; BMS/Pfizer), and the antithrombin inhibitor dabigatran etexilate (Pradaxa/Pradaxa; Boehringer Ingelheim International).

Factor Xa Inhibitors (Rivaroxaban and Apixaban)

The clinical pharmacology of rivaroxaban, apixaban, and dabigatran is shown in Table 10.1.
Rivaroxaban is a direct inhibitor of activated factor X.\textsuperscript{114,164,166} It has about 80% absorbability, and peak blood levels appear within 2 to 3 hours.\textsuperscript{166,169} The terminal half-life is 7 to 11 hours. Approximately 33% of the drug is eliminated by the kidney. Following an oral dose of rivaroxaban, there is a direct relationship between pharmacodynamic effects and the degree of renal impairment.\textsuperscript{166} In patients with severe renal insufficiency (CrCl < 30 mL/min), the area under the curve (AUC), indicating increased rivaroxaban concentration, was increased by 1.2 to 2.2.\textsuperscript{166} For this reason, rivaroxaban must be used with caution in patients with moderate renal impairment (CrCl 30–49 mL/min), and it is contraindicated with a CrCl < 30 mL/min.\textsuperscript{166} The pharmacokinetic/pharmacodynamic (PK/PD) profile of rivaroxaban is dose dependent and predictable, with no change with age, sex, or body weight.\textsuperscript{169} In clinical trials there has been no evidence of liver or other toxicities and no increase in vascular events such as myocardial infarction, stroke, or peripheral thrombosis.\textsuperscript{169}

Apixaban is also a direct inhibitor of factor Xa, with an oral availability of about 50%.\textsuperscript{112,114,167–172} Peak blood levels are seen within 3 to 4 hours, and the terminal half-life is 8 to 12 hours. Approximately 27% of the drug is eliminated by the kidney. Apixaban dose adjustment is not required for patients with mild to moderate renal impairment, but it is contraindicated in a patient with a CrCl < 30 mL/min.\textsuperscript{167} No dose adjustment is required for age or weight, and in clinical trials there is no evidence of hepatic or other toxicities and no increase in the incidence of vascular events.\textsuperscript{167}

**Table 10.1 Clinical Pharmacology of Apixaban, Rivaroxaban, and Dabigatran**

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct factor Xa inhibitor</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td>Absolute availability</td>
<td>~ 50%</td>
<td>~ 100%</td>
<td>~ 6.5%</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Food effect</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>~ 27%</td>
<td>~ 33%</td>
<td>85%</td>
</tr>
<tr>
<td>Mean T\textsubscript{1/2}</td>
<td>12 h</td>
<td>5–13 h</td>
<td>11 h (healthy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14–17 h (patients)</td>
</tr>
<tr>
<td>T\textsubscript{max}</td>
<td>3–4 h</td>
<td>2–4 h</td>
<td>0.5–2 h (healthy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7–9 h (patients)</td>
</tr>
</tbody>
</table>

*Note: There have been no direct comparisons between apixaban, rivaroxaban, or dabigatran. This information is derived from the product monographs of these agents. For further information, refer to the product monographs and the text.*

Apixaban Product Monograph.\textsuperscript{167}

Rivaroxaban Product Monograph.\textsuperscript{166}

Dabigatran Product Monograph.\textsuperscript{168}

**Factor II Thrombin Inhibitor (Dabigatran)**

Dabigatran etexilate is a prodrug that is rapidly converted to active dabigatran in the liver following absorption.\textsuperscript{112,114,164,165,168,173–177} Bioavailability is about 6.5%, and
peak blood levels are reached within about 2 hours. The terminal half-life is about 14 to 17 hours, with most of the drug (80%) eliminated through the kidney unchanged. There is a direct correlation between the systemic exposure to dabigatran and the degree of renal insufficiency. Moderate renal impairment (CrCl 30–50 mL/min) increased the AUC twofold, whereas severe renal impairment (CrCl < 30 mL/min) increased it sixfold. Dabigatran has predictable PK/PD profiles without any influence of weight or sex and no food interactions. Dabigatran is not metabolized through the cytochrome P-450 3A4 (CYP3A4) pathway, but inhibitors or inducers of P-glycoprotein can affect drug levels. Dabigatran should be used with caution in patients with CrCl between 30 and 49 mL/min, and it is contraindicated in those with a CrCl < 30 mL/min. It is recommended that CrCl measurements be made before starting dabigatran and periodically during treatment, particularly in elderly patients with borderline renal function. In clinical trials and in practice, dabigatran treatment has been complicated by dyspepsia, which has led to the discontinuation of treatment in several patients. There is also a higher incidence of lower gastrointestinal bleeding, which may be related to the high concentration of active dabigatran excreted in the stool. A higher rate of myocardial infarction has been observed in two clinical trials of dabigatran when compared with warfarin and enoxaparin treatment. A meta-analysis of seven clinical trials of dabigatran supported the findings of the individual trials. Because dabigatran has been widely used, there have been reports of excessive bleeding in the medical literature and in reports to the Food and Drug Administration (FDA). There is concern that the drug effect cannot be blocked; for example, patients who are elderly with borderline renal function that may rapidly deteriorate are those most at risk for excessive bleeding on this drug.

Measuring the Anticoagulant Effect of the New Oral Anticoagulants

Although routine monitoring of the drug effect for the new oral anticoagulants (NOACs) is not required, there are times when it is important to assess the drug effect for a risk of bleeding or thrombosis. Examples of such occasions are the need for emergency or urgent intervention for surgery, serious bleeding or a thrombotic event, worsening renal or hepatic function, suspected overdosing, or drug interactions. An elevated aPTT or prothrombin time (PT) can provide qualitative evidence of the presence of dabigatran or the factor Xa inhibitors, respectively, but each lacks sensitivity for a quantitative evaluation. A calibrated prothrombin time using a neoplastin or neoplastin plus reagent can provide a good correlation with plasma concentration of rivaroxaban, but there are no data on apixaban plasma levels with this test. For both factor Xa inhibitors, the most reliable measure of plasma levels is a chromogenic Xa level, which is available in most larger centers. However, at this time there are no studies correlating Xa levels taken at peak or trough times with either bleeding or thrombotic events. The best test available to measure the drug levels of dabigatran is the dilute thrombin time (DTT), which is now commercially available (the Hemoclot test). A normal DTT indicates no detectable dabigatran, and an elevated level (e.g., > 200 ng/kg) indicates an increased risk of bleeding. At this time there are no data to indicate a safe plasma drug level for surgical intervention. When interpreting the results of these laboratory tests, it is essential to know
the timing of the last dose, the dosage used, the level of renal and hepatic function, and the risk of bleeding.

**Management of Emergency Situations Requiring Reversal of the Anticoagulant Effect**

When possible, the most effective approach to an intervention is to delay the procedure until the drug effect is gone (e.g., 12 to 24 hours depending on the level of renal function and the required level of hemostasis). In urgent situations, general measures include fluid replacement, which may consist of packed red blood cells, platelets, fresh frozen plasma, colloids, surgical hemostasis, or compression if possible.\(^\text{165}\) In the emergency situation prothrombin complex concentrates (PCCs) or activated factor VII may be given.\(^\text{165,186–189}\) There is no evidence that PCCs block the anticoagulant effect of dabigatran in humans, but in healthy volunteers the anticoagulant effect of rivaroxaban was effectively blocked by PCC.\(^\text{186}\) However, there are no data on the effect of PCCs in patients with serious bleeding. There is early evidence that a catalytically inactive factor Xa that can bind to the direct factor Xa inhibitors can reverse the anticoagulant activities of rivaroxaban or apixaban.\(^\text{191}\) There is little to support the use of activated factor VII (e.g., NovoSeven in either the Xa or thrombin inhibitors).\(^\text{165}\)

In patients on hemodialysis who received dabigatran prior to dialysis, the drug level was lowered by 60% after 2 hours' treatment, and there are case reports supporting the role of hemodialysis in this setting.\(^\text{165,168}\) There is preliminary evidence that an antibody against dabigatran and a hapten can effectively block the anticoagulant activity of dabigatran.\(^\text{168}\)

**Interruption of Treatment with the New Oral Antithrombotic Agents**

When the factor Xa or IIa inhibitors must be discontinued for procedural reasons, such as surgery, biopsies, or insertion of a pacemaker, it is recommended that the drug should be stopped in time to allow four to five drug half-lives before the procedure, particularly if minimal drug effect is required.\(^\text{165–167}\) For dabigatran, this translates into 3 days before surgery if the CrCl > 50 mL/min and 4 to 5 days for a CrCl of 30 to 49 mL/min.\(^\text{167}\) For rivaroxaban and apixaban in patients with mild to moderate renal impairment (CrCl > 50 mL/min), the last dose should be given 3 days before surgery. In patients in whom a mild to moderate anticoagulant effect of the drug is acceptable, the drug may be continued for an extra day before discontinuing.\(^\text{165,166}\) When the drugs are to be resumed, it is recommended that they be delayed for at least 48 hours after major surgery and 24 hours after minor surgery. In all cases, the determination of risk of bleeding must be weighed against the risk of thrombosis.\(^\text{165–168}\)

**New Oral Anticoagulants in the Treatment of Venous Thromboembolism**

All three agents have been compared with standard VKA therapy for the prevention of stroke and atrial fibrillation\(^\text{178,189,190}\) and for the initial and extended treatment
Dabigatran, rivaroxaban, and apixaban are available for use in several countries for the prevention of stroke in patients with atrial fibrillation. Dabigatran and rivaroxaban have been approved or are under review for treatment of DVT and PE, whereas clinical trials in the treatment of VTE with apixaban are just being reported.

In the Einstein DVT and PE studies, rivaroxaban 15 mg twice daily was administered for 3 weeks followed by 20 mg once daily and compared with standard VTE therapy with a targeted INR of 2 to 3. Although there was no initial use of LMWH bridging in the rivaroxaban arm, patients were eligible for the study if they had received therapeutic doses of LMWH, fondaparinux, or UFH for less than 48 hours or if they had received no more than a single dose of VKA therapy before randomization. In the Einstein DVT study, rivaroxaban was shown to be noninferior to VKA therapy in the prevention of recurrent VTE with similar bleeding rates. In patients who had completed 6 to 12 months of treatment with rivaroxaban, this agent was compared with placebo in the prevention of recurrent VTE for an additional 6 to 12 months. Rivaroxaban significantly reduced the incidence of VTE in these patients, but there was an increase (nonsignificant) in major bleeding. In the Einstein PE study, rivaroxaban was shown to be noninferior to warfarin in the prevention of recurrent VTE. The rates of the principal safety end point of a composite of major and nonmajor clinically relevant bleeding were similar, but the rates of major bleeding alone were significantly reduced by rivaroxaban.

Three studies have been reported on the use of dabigatran etexilate in the treatment of VTE. In the RE-COVER trial, dabigatran 150 mg twice daily was compared with standard warfarin therapy with a targeted INR of 2 to 3. Patients presenting with VTE were given parenteral anticoagulation therapy with UFH or LMWH for 8–10 days before either the dabigatran etexilate or warfarin were started. Treatment continued for 6 months without follow-up for 30 days following that period. Dabigatran was shown to be noninferior to the standard VKA therapy in the prevention of recurrent VTE or VTE-related death, and the incidence of major bleeding was comparable. The incidence of the composite of major and nonmajor clinically relevant bleeding, however, was significantly less with dabigatran. In two studies on the extended treatment of VTE, dabigatran when compared with warfarin had decreased recurrent VTE and resulted in less major and clinically relevant nonmajor bleeding. However, there was a higher incidence of acute coronary syndromes, as had been recorded in previous trials comparing dabigatran with warfarin. When compared with placebo, the incidence of recurrent VTE was lower, but the incidence of clinically relevant nonmajor bleeding was higher.

Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months was compared with conventional treatment (LMWH followed by warfarin) for 6 months. The incidence of VTE and VTE-related death was noninferior with apixaban therapy, and there was significantly less major bleeding and a composite of major and clinically relevant nonmajor bleeding.

When these new oral antithrombotic agents become available for the treatment of VTE, they will provide a convenient alternative to VKA therapy, particularly in those in whom anticoagulant management is difficult or impossible to achieve. Until there is more experience with the new oral antithrombotic agents, they would not be recommended for the treatment of VTE associated with neurosurgical conditions such as brain tumors, intracranial bleeding, traumatic brain
Thrombolysis or Mechanical Fragmentation for the Treatment of Proximal Deep Vein Thrombosis and Pulmonary Embolism

Recent clinical trials on the use of catheter-directed thrombolysis (CDT), with or without mechanical thrombus fragmentation, in patients who have extensive iliofemoral DVT, have shown that CDT improves vein patency and venous valve function in the initial and follow-up period in a number of these patients. Furthermore, there is evidence that CDT can reduce the incidence of the PTS and can improve the quality of life in these patients. Operative thrombectomy has been shown to improve vein patency with less leg swelling and fewer venous ulcers when compared with anticoagulation alone. Patients with iliofemoral DVT who are candidates for these more invasive approaches to therapy include those with DVT of less than 14 days’ duration, particularly if venous gangrene is imminent, who have good functional status, and who are at low risk of bleeding. Following the initial treatment, patients are treated with anticoagulations in the usual way. CDT may cause less major bleeding and, in particular, a lower incidence of intracranial hemorrhage than systemic thrombolysis. At this time the ACCP recommendation is for anticoagulation therapy over CDT, systemic thrombolysis, or venous thrombectomy.

Although individual studies and meta-analyses of various studies comparing systemic thrombolysis with heparinization alone in patients with PE have demonstrated improvement in pulmonary vascular resistance with thrombolysis but no mortality advantage, there are many contraindications to systemic thrombolysis, including intracranial bleeding or recent stroke, recent surgery or trauma, pregnancy, cancer, recent needle biopsy of internal organs, and hemostatic defects. The use of systemic or local thrombolysis for the treatment of submassive PE should only be undertaken after careful consideration of the risk/benefit of the procedure to the patient. Mechanical dissolution of the embolus may be carried out in conjunction with thrombolysis.

Inferior Vena Cava Filter

Insertion of a removable or permanent inferior vena cava (IFC) filter is indicated for patients who have an acute VTE and have an absolute contraindication to anticoagulation, such as major bleeding or objectively documented recurrent VTE during adequate anticoagulation therapy. Although IVC filters have not been shown to decrease mortality, they can effectively prevent important pulmonary embolism. In follow-up studies, although there is a decreased incidence of PE, there is an increased incidence of recurrent DVT and IVC filter thrombosis. There is also evidence that IVC filter use may increase the incidence of the PTS. Long-term anticoagulation therapy should be started as soon as safely possible after placement of a vena cava filter and continued for the duration of treatment as for patients without an IVC filter.
Treatment of Venous Thromboembolism in Neurosurgery Patients

There have been numerous clinical trials and meta-analyses of the prevention of VTE in neurosurgical patients. These include patients with traumatic brain injury, intracranial hemorrhage, craniotomy for brain tumors, traumatic head injuries, and central nervous system lymphomas. For most patients, the use of LMWH, with or without sequential compression devices, has been the recommended approach to thromboprophylaxis.

There has been a paucity of clinical trials and observational studies on the treatment of VTE in these patients. In all patients the risk of inducing or promoting intracranial bleeding must be weighed against the risk of VTE and, in particular, death from PE. In patients at high risk of bleeding who have VTE, the ACCP recommends anticoagulant treatment for only 3 months.

Systemic thrombolysis is contraindicated in neurosurgical patients, and any form of anticoagulation is contraindicated when there is active intracranial bleeding. Anticoagulant therapy should be used with caution in patients with recent intracranial surgery, those with preexisting hemostatic defects such as thrombocytopenia, those who are at high risk of falls, and those who have poor compliance with medical therapy. However, patients with an intracranial tumor or brain metastases without evidence of active bleeding and who have VTE are candidates for anticoagulant therapy because of the high incidence of fatal PE. These patients require careful monitoring to limit the risk of bleeding complications, particularly with over-anticoagulation.

There have been a number of reports of the use of anticoagulants or vena caval filters (or both) in patients with primary or secondary brain tumors and the presence of VTE. Most studies are retrospective, with small numbers of patients; none are randomized, and the patient populations are heterogeneous. Anticoagulant therapy consisted of UFH in various doses or LMWH for short- or long-term use. In some cases VKA therapy has been added. Reported rates of recurrent VTE and bleeding have been low, and in particular the more recent reports have recorded low or absent incidence of intracranial hemorrhage.

In one study the use of vena caval filters alone resulted in a high incidence of thrombotic complications (VTE and filter thrombosis). In a nonrandomized study comparing patients who had IVC filters or anticoagulant therapy, there was no differences in in-hospital or overall mortality between the two treatment groups. In a recent retrospective review of the use of LMWH in patients with brain metastases and VTE or superficial thrombosis, there was no evidence of clinical or radiographic findings of intracranial hemorrhage.

Based on evidence from randomized clinical trials, it has been recommended that patients with VTE and cancer should receive treatment with LMWH for 3 to 6 months. Following this initial treatment, the decision must be made as to whether to continue LMWH or switch to oral anticoagulant therapy. At this time the use of the new oral anticoagulants is not recommended. In those patients with ongoing metastatic malignancy including brain metastases, the recommendation is to continue LMWH therapy. In patients with proximal DVT in the presence of active bleeding or a high risk of bleeding, a retrievable IVC filter may be inserted until the risk of bleeding subsides, at which time the filter can be removed and anticoagulant therapy may be started.
In the absence of data from randomized clinical trials, patients with primary or secondary brain tumors who also have VTE must be considered for treatment on a case-by-case basis with respect to bleeding risk. In those patients who are candidates for active treatment of the VTE, the judicious use of LMWH with or without insertion of an IVC filter offers the most acceptable approach.

**Thrombosis in Unusual Locations**

Although DVT usually occurs in the deep veins of the lower extremities, thrombosis may occur in a number of unusual locations.\(^7,8,44,218\) Upper extremity DVT (UEDVT) may involve the axillary and more proximal veins, and the treatment with LMWH and VKA therapy is recommended rather than no treatment or thrombolytic treatment.\(^44,218\) If thrombolysis is administered, patients should undergo anticoagulation in the usual intensity and duration as for those who do not have thrombolysis treatment. When UEDVT is associated with central venous catheters, the recommendation is to leave the catheter in place if it is functional, and to initiate the anticoagulation for a period of at least 3 months.\(^111\) The same recommendation for 3 months of anticoagulation applies to patients in whom the catheter is removed or left in situ and for those with an underlying malignancy.\(^111\)

Isolated iliac vein thrombosis may occur spontaneously or as a result of iliac vein compression in pregnancy or in the May-Thurner syndrome.\(^71,72\) Depending on the circumstances, treatment may include thrombolysis with mechanical thrombectomy or, in the case of the May-Thurner syndrome, stenting of the involved narrowed segment of the iliac vein.\(^71–73\) Otherwise, treatment with LMWH and VKA is recommended.

Thrombosis may occur in the splanchnic bed involving the portal splenic and mesenteric veins. If these are symptomatic they require anticoagulation therapy for at least 3 months or until the original thrombosis has resolved.\(^111\) For thrombosis found incidentally in patients who are not symptomatic, no anticoagulation therapy is recommended.\(^111\)

For patients with calf vein thrombosis distal to the popliteal vein, the recommendation is to treat with anticoagulant therapy for at least 3 months or to follow-up with repeat ultrasound.\(^4,111\)

Although superficial vein thrombosis has been considered a relatively benign disorder that has been treated with nonsteroidal anti-inflammatory drugs, compression stockings, and rest, there is evidence that superficial vein thrombosis (SVT) can have more serious consequences, such as the development of PE and proximal DVT, especially when it involves the veins in the thigh.\(^9,219\) This is particularly true for SVT of the lower limb of at least 5 cm in length if it is in close proximity to the groin. In such patients, the use of prophylactic doses of fondaparinux or LMWH when compared with placebo significantly decreased extension of the original SVT.\(^219\) Patients who have extensive SVT close to the saphenofemoral junction, a history of previous DVT or SVT, active cancer, or recent surgery are candidates for prophylactic anticoagulation treatment for up to 45 days.
KEY POINTS

- The serious consequences of VTE are fatal pulmonary embolism, post-thrombotic syndrome, chronic thromboembolic hypertension, and paradoxical cerebral embolism.
- Postthrombotic syndrome occurs more commonly in patients with recurrent ipsilateral iliofemoral DVT and in those who have inadequate anticoagulation in the early state of treatment.
- Thrombophilias include factor V Leiden, prothrombin mutant, antithrombin deficiency, protein C or S deficiency, and antiphospholipid antibody syndrome.
- Common risk factors for VTE in neurosurgery:
  ◦ Craniotomy (particularly for brain tumor
  ◦ Higher grade malignancy
  ◦ Metastatic malignancy
  ◦ Chemotherapy or radiation therapy
  ◦ Immobilization
  ◦ Multiple trauma
  ◦ Advanced age
- Clinical signs and symptoms for VTE are nonspecific and diagnosis must include objective diagnostic tests that have been properly validated.
- Objective tests for DVT:
  ◦ Compression ultrasound (US) is the most useful test for the diagnosis of DVT with high sensitivity and specificity for symptomatic proximal DVT.
  ◦ Complete compression US can detect distal DVT in symptomatic patients.
  ◦ Ascending contrast venography may be occasionally required for the diagnosis of recurrent DVT or when repeat US is impractical or inconclusive.
  ◦ CT or MRI venography may be helpful in diagnosing DVT proximal to the inguinal ligament (e.g., isolated iliac vein thrombosis, with pregnancy or with vessel anatomical abnormalities/defects such as May-Thurner syndrome).
- Objective tests for PE:
  ◦ Multidetector CT angiography is the diagnostic test of choice, with a high sensitivity and specificity for the diagnosis of symptomatic PE.
  ◦ Adding CT venography to CTA increases the sensitivity.
  ◦ VQ scanning has a role in the diagnosis of PE in patients with renal insufficiency, those who have allergy to contrast agents, and in younger women because of the concern about radiation exposure to the breasts with CTA.
  ◦ MRI angiography has a limited role in the diagnosis of PE in pregnancy but has not become routine.
  ◦ Pulmonary angiography is occasionally required (e.g., when a positive diagnosis is urgently needed in ICU patients).
- Echocardiography and biomarkers assess right heart strain and can determine which patients with PE may benefit from early thrombolysis/mechanical dissolution therapy.
- Treatment of venous thromboembolism:
  ◦ Standard therapy: initiate LMWH or UFH and warfarin therapy simultaneously. Continue for at least 5 days or until INR is in the therapeutic range for 2 consecutive days.
Monitor the warfarin effect with the INR starting on day 3 and periodically throughout treatment for at least 3 months, although extended or long-term treatment may be indicated.

Alternative therapy strategy: LMWH in therapeutic doses once or twice daily for at least 3 months (may be followed by warfarin therapy or continued LMWH).

LMWH is the recommended treatment of cancer-related VTE and is the preferred approach to VTE treatment in neurosurgery.

- Catheter-directed thrombolysis (CDT) with or without mechanical clot dissolution:
  - Indicated in proximal DVT with impending vascular insufficiency.
  - May be indicated in isolated iliofemoral DVT of recent onset (7–14 days) if there is good functional status and low risk of bleeding.
  - May be indicated in patients with submassive PE with none of the usual contraindications.

- D-dimer test to exclude VTE:
  - A quantitative D-dimer test with a rapid turnaround (e.g., ELISA assay) is the most useful.
  - A negative D-dimer test result has a very high negative predictive value in excluding VTE.
  - Most hospitalized patients have a positive D-dimer, rendering it of little use excluding VTE.
  - The combination of a D-dimer and a pretest probability test directs the diagnostic management of VTE.

- Removable or permanent IVC filters are usually indicated in patients with VTE who have absolute contraindications to anticoagulants or who have major bleeding while anticoagulated and in some cases of extension or new thrombus formation while anticoagulated.

- Treatment of VTE in neurosurgery patients:
  - First weigh the risk of bleeding (especially intracranial) against the risk of fatal PE.
  - In most cases, long-term LMWH is the preferred approach as opposed to warfarin treatment.
  - Use of systemic or regional thrombolysis is contraindicated.
  - Use of fondaparinux or the new anticoagulants are strongly discouraged because of the difficulty in blocking the anticoagulant effect (particularly so with fondaparinux and dabigatran).
  - Use of an IVC filter ± anticoagulants is an alternative approach.
  - Future prospective clinical trials are clearly indicated to determine the appropriate management.
REVIEW QUESTIONS

1. Regarding serious complications of VTE, are the following statements true or false?
   A. Fatal pulmonary embolism is rare.
   B. Most fatal PE occurs suddenly and without warning.
   C. Postthrombotic syndrome (PTS) occurs more commonly in patients with recurrent ileofemoral DVT.
   D. Graduated compression stockings may decrease the risk of PTS.
   E. Chronic thromboembolic hypertension occurs in 5% of patients with PE.

2. Which of the following is/are thrombophilias (i.e., they increase the risk of VTE)?
   A. Antithrombin deficiency
   B. Protein C or S excess
   C. Factor VII Leiden
   D. Antiphospholipid antibody syndrome
   E. Prothrombin mutant

3. Which of the following is/are risk factors for VTE in neurosurgery?
   A. Craniotomy
   B. Lumbar discectomy
   C. Immobilization
   D. Young age
   E. Trauma

4. Regarding the diagnosis of VTE, are the following statements true or false?
   A. Clinical signs and symptoms are specific and sensitive.
   B. The Wells rule is used to determine pretest probability for the diagnosis of DVT.
   C. D-dimer measurement has no reliable role in pretest probability for the diagnosis of DVT.
   D. Compression ultrasound is the most useful test for the diagnosis of DVT.
   E. Chest CTA is the test of choice for the diagnosis of symptomatic PE.

5. Regarding the treatment of VTE, are the following statements true or false?
   A. Standard therapy involves initiation of LMWH or UFH and warfarin simultaneously.
   B. Standard therapy involves maintaining LMWH or UFH and warfarin until the INR is in the therapeutic range for 5 days.
   C. The INR should be monitored daily with the start of warfarin therapy.
   D. Alternative therapy involves treatment with LMWH in therapeutic doses for 3 to 12 months.
   E. Warfarin is the recommended treatment of cancer-related VTE.

6. True or false?
   A. The main adverse effects of UFH are bleeding, thrombocytopenia, and osteoporosis.
   B. Heparin-induced thrombocytopenia usually occurs in the first 4 to 10 days after commencing therapy.
C. Warfarin should be discontinued 5 days before a surgical procedure to allow the INR to return to normal.

D. The new anticoagulant agents rivaroxaban, apixaban, and dabigatran are safe with standard dosing in patients with renal impairment.

E. The anticoagulant effects of the new anticoagulant agents rivaroxaban, apixaban, and dabigatran are reversed with fresh frozen plasma and vitamin K.

7. Regarding inferior vena cava filters, are the following statements true or false?

A. They are the standard of care for prophylaxis of PE in all neurosurgical patients.

B. They are permanent devices.

C. They prevent DVT.

D. They are indicated in patients with an absolute contraindication to anticoagulation.

References


An Introduction to the Rationale for Mechanical and Chemical Deep Venous Thrombosis Prophylaxis in Neurosurgery Patients

Venous thromboembolism (VTE) is a broad term that encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE is a preventable cause of severe morbidity and mortality in neurosurgery patients, who are unique in regard to VTE in two very important aspects.

First, many neurosurgery patients are at an increased risk for VTE development—perhaps second only to orthopedic surgery patients—because of immobility, hypercoagulability, and endothelial damage, which are the tenets of Virchow’s classic triad of thrombosis. The immobility is a necessary consequence of the comatose or para/tetraplegic state induced by many of the pathologies routinely treated with neurosurgery (e.g., high-grade subarachnoid hemorrhage, severe traumatic brain injury, hydrocephalus, spinal cord injury/tumor). Hypercoagulability is an unfortunate consequence in neuro-oncological patients, particularly those with malignant brain tumor or meningioma. Endothelial damage may be induced either through trauma or the neurosurgical operation itself.

The second unique aspect of VTE to the neurosurgical patient is that any intracranial hemorrhage (ICH) or spinal epidural hematoma as a consequence of VTE chemoprophylaxis can be a source of significant morbidity and mortality. This consequence is unique to neurosurgical patients and often leads to confusion and greater risk when nonneurosurgical physicians manage neurosurgical patients without appreciating this element of neurocritical care.

Mechanical prophylaxis, which includes compressive stockings and sequential compression devices (SCDs), is uniformly recommended for all neurosurgical patients regardless of the type of procedure undertaken. The risks are minimal with stockings and SCDs, whereas the potential gains are substantial. Although the use of SCDs has not been compared with the absence of treatment in a randomized trial, the incidence of VTE in neurosurgical patients with only mechanical prophylaxis has been studied. Naturally, the incidence of DVT in mechanical-only prophylaxis varies linearly with the intensity of screening methods (i.e., using duplex ultrasonography in a patient only when symptoms are present versus routine regular screening) from 3.2 to 43%.1–11 The average incidence is around 25% in studies with routine screening. Similarly, the exact conversion rate of DVT to PE is unknown and varies with screening technique, but is estimated to be 0.5 to 5%. PEs
carry approximately an 18 to 60% mortality rate, and there are other well-known risks for patients treated with systemic anticoagulation, including gastrointestinal hemorrhage, skin necrosis, systemic allergic responses, and renal failure.

The most up-to-date guidelines recommend chemical DVT prophylaxis for surgical patients “once the risk of bleeding diminishes.” Thus, the crux of the issue is when does the risk of bleeding become outweighed by the risk of VTE? The answer is not straightforward, but here we review each subset of neurosurgical patients routinely encountered in practice, with final recommendations at the conclusion of each subset (summarized in Table 11.1).

<table>
<thead>
<tr>
<th>General Guidelines for DVT Prophylaxis in Neurosurgical Subpopulations</th>
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<td><strong>Type of Patient</strong></td>
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<td>Pediatric patients</td>
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*High-risk features: Surgery > 6 hours, malignancy, prolonged immobility
**Complex spine-specific high-risk features: history of VTE, malignancy, known hypercoagulability, prolonged immobilization > 2 weeks, staged procedures > 5 levels, combined anterior-posterior approaches, iliocaval manipulation during exposure, planned anesthetic time > 8 hours

Abbreviations: IVC, inferior vena cava; LMWH, low molecular weight heparin; SCI, spinal cord injury; TBI, traumatic brain injury; UFH, unfractionated heparin; VTE, venous thromboembolism.
Deep Vein Thrombosis Prophylaxis in Adult Craniotomy Patients

Incidence of DVT

Browd et al\textsuperscript{16} reviewed the major studies that have examined the incidence of VTE and ICH in neurosurgical patients on DVT prophylaxis undergoing craniotomy. Since that review, only one other large series has been published,\textsuperscript{8} and it confirmed the conclusions that the incidence of VTE in patients receiving chemical DVT prophylaxis is always reduced compared with patients receiving mechanical compression only, and that the rate of VTE in patients receiving chemical prophylaxis is 0 to 18.7%, with a mean of around 15% for patients routinely screened with duplex. Thus, the relative risk reduction of DVT when using subcutaneous chemoprophylaxis is 18 to 82%, with an average of 40%.\textsuperscript{1–11} Additionally, the rate of ICH in the nonchemically treated groups was 0 to 4.3%, compared with 0 to 10.9% in patients receiving chemical prophylaxis. When patients who were treated preoperatively with chemical prophylaxis are excluded, the ICH range drops to a more reasonable level of 0 to 2.6%. This range is still wide and is the main reason why creating a risk/benefit analysis is so difficult. Indeed, a decision analytic model dealing with this variability using both sensitivity analysis and Monte Carlo simulation\textsuperscript{17} found, rather surprisingly, that mechanical prophylaxis only yielded superior outcomes compared with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) in patients undergoing craniotomy. There were, however, significant assumptions made when “rating” the effective quality-of-life effects of DVT, PE, and ICH—thus making this conclusion rather arbitrary.

Timing and Type of DVT Prophylaxis

The timing and type of chemical DVT prophylaxis—UFH or LMWH—after craniotomy is another area of controversy. Contrary to recommendations in other surgical cohorts, routine preoperative DVT prophylaxis in neurosurgical patients is not recommended because of the unacceptably high ICH rate demonstrated in older studies.\textsuperscript{14} Furthermore, many institutions have a rather arbitrary protocol of waiting 12 to 48 hours after surgery before starting subcutaneous chemical DVT prophylaxis. This postoperative “waiting period” is intended to reduce the incidence of postoperative ICH by allowing adequate hemostasis before beginning DVT prophylaxis. Any immediate postoperative ICH on computed tomography scan would usually warrant an extension of this waiting period.

Only a handful of studies have evaluated the type and timing of postoperative DVT chemical prophylaxis. LMWH has a greater anti–factor Xa/anti–factor IIa activity, greater bioavailability, more predictable anticoagulatory effects, and longer duration of action than UFH. None of the various forms of LMWH has been routinely proven superior to another. Given this information, LMHW has replaced UFH in general surgery and internal medicine patients; however, UFH is still very popular for postoperative use in neurosurgical patients because of the older studies that suggest a possible elevated ICH rate in LMWH.

In 2000, Iorio and Agnelli\textsuperscript{18} published a meta-analysis of the LMWH risk/benefit in neurosurgical patients. They found that, on average, LMWH reduced the relative
rate of DVT by 38%, which was in accordance with previous studies, with a major ICH rate of 2.2%. The authors concluded that for every 11 thrombotic events prevented by LMWH, one major nonfatal ICH would occur.

Khaldi et al8 studied the risk of hemorrhage and DVT in patients receiving UFH 24 or 48 hours postoperatively. They found no difference in VTE or ICH in either group, with a DVT incidence of 16%. Additionally, they found that 92% of DVTs occurred in the first 2 weeks after surgery, and the incidence had a linear relationship to the length of surgery, with a statistically significant increased risk of PE in surgeries lasting > 6 hours.

**Recommendations**

No craniotomy patient should be treated with preoperative subcutaneous heparin for the sake of improving DVT prophylaxis. All patients should receive intraoperative and postoperative mechanical DVT prophylaxis. Subcutaneous UFH chemoprophylaxis should be initiated 24 to 48 hours postoperatively to reduce the risk of DVT by 40%. If the surgery lasts longer than 6 hours or other high-risk features are present (malignancy or prolonged immobility), an initial use of or switch to subcutaneous LMWH can be considered, weighing against the slightly higher risk of hemorrhage.

**Deep Vein Thrombosis Prophylaxis in Traumatic Brain Injury**

**Incidence of DVT in Traumatic Brain Injury**

Serious head injuries are an independent risk factor for DVT. The rate of DVT in patients with moderate to severe traumatic brain injury (TBI) is up to 33%.19–23 Different causes, such as increased circulating levels of tissue factor and von Willebrand factor, have been proposed, but the exact reasons remain unclear. Interestingly, even with properly initiated chemoprophylaxis, the rate of DVT formation in patients with severe head injury is three to four times higher than in matched controls.23 To compound matters further, Norwood et al24 reported an intracranial bleeding risk of 9.1% in patients with TBI who required craniotomies when enoxaparin prophylaxis was initiated within 24 hours of the procedure.

**Timing and Type of Chemoprophylaxis in Traumatic Brain Injury**

Choosing when to initiate chemoprophylaxis in the TBI patient is difficult, as is choosing the type of heparin to use. The risk of development of DVT has to be cautiously weighed against the potentially increased risk of bleeding complications; however, the literature is quite clear on a few key issues. First, withholding DVT chemoprophylaxis for > 48 hours after TBI resulted in a fivefold increase in the rate of DVT.23 Additionally, in analyzing the results in all trauma patients together, UFH administered every 8 hours has proven noninferior to LMWH every 12 hours in a large prospective study.25 This information, coupled with the results of the study by Norwood et al24 on LMWH, suggests that UFH should be initiated in all trauma
patients within 48 hours of admission. Additionally, because the risk of DVT is high even on chemoprophylaxis, aggressive screening with weekly Doppler ultrasonography should be considered. If chemoprophylaxis cannot be initiated, the use of an inferior vena cava (IVC) filter (as described below) should be considered. Extended DVT prophylaxis during inpatient rehabilitation can be considered in patients with TBI, but the rate of new DVT after an inpatient stay is only 2 to 5%.26

**Recommendations**

The use of UFH every 8 hours should be initiated in all TBI patients within 48 hours of admission. Screening with weekly Doppler ultrasound examinations should be considered. If chemoprophylaxis cannot be initiated, the use of an IVC filter should be strongly considered.

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**Incidence of Deep Vein Thrombosis in Traumatic Spinal Cord Injury**

**Incidence of DVT**

The reported incidence of DVT in patients with spinal cord injury (SCI) varies widely depending on the screening method used, with rates ranging from 9 to 100%.27 Notably, VTE causes nearly 10% of all deaths in the first year after SCI. The cause for such an increased risk is multifactorial, but again harkens back to Virchow’s triad of stasis, hypercoagulability, and vessel intimal injury. Additional pathophysiological mechanisms have also been proposed, including impaired circadian variations of hemostatic and fibrinolytic parameters and changes in platelet function and fibrinolytic activity.28

**Type and Timing of DVT Prophylaxis**

Previous systematic review has suggested that LMWH is almost three times as effective as UFH in preventing DVT in the SCI population,29,30 but the same is not necessarily true with PE. Additionally, only a handful of studies have investigated the timing of early versus late administration of subcutaneous DVT prophylaxis. One of these studies found a 10-fold increase in DVT when LMWH was started > 72 hours after injury.31 As for duration of prophylaxis in SCI patients, level III evidence suggests that nearly 90% of all DVTs in patients with SCI occur within the first 3 months, and studies have confirmed the utility of chemoprophylaxis for this time frame.32 If the patient has a known history of VTE, 6 months of chemoprophylaxis should be considered.

**Recommendations**

Patients with SCI are arguably at the highest risk for VTE of any neurosurgical subgroup. The SCI patient should have LMWH initiated within 72 hours of injury for a total of at least 12 weeks. If chemoprophylaxis with LMWH cannot be initiated, an IVC filter should be strongly considered. Chemical prophylaxis should be stopped 24 hours before any planned surgery and resumed 24 hours after.
Deep Vein Thrombosis Prophylaxis in Adult Patients Undergoing Elective Spinal Surgery

Incidence of DVT

One large meta-analysis has been performed on studies of patients undergoing elective spine surgery. As with cranial patients, screening protocols and methods varied, making definitive conclusions difficult, but this meta-analysis found that the rate of DVT in patients undergoing elective spine surgery is 6% when no prophylaxis is used, 2% when mechanical prophylaxis is used, and < 0.01% when mechanical prophylaxis and LMWH are used. The results are similar in the cervical and the thoracolumbar spine. Patients undergoing a combined anterior and posterior reconstruction have the highest absolute rate of DVT (14–18%), but the small sample sizes in these studies prevented drawing definitive conclusions. The incidence of PE in the published series of patients undergoing elective spine surgery was exceedingly low at 0.06%. The incidence of postoperative epidural hematoma was 0% in the group that did not receive any chemical prophylaxis compared with 0.4% in the LMWH group, with 38% of those patients developing permanent defect. Similar data have been confirmed by other, more recent literature reviews as well. The use of preoperative IVC filters has been studied in elective spinal reconstruction patients. These important data and clinical recommendations are discussed later in this chapter.

Recommendations

For the patient undergoing elective spine surgery that does not involve a major spinal reconstruction, mechanical prophylaxis alone is sufficient DVT prophylaxis. If other high-risk features are present (malignancy or prolonged immobility) and there is no contraindication to heparin, subcutaneous chemical prophylaxis should be considered for 24 to 48 hours postoperatively. Spine reconstruction patients face different risks, which are discussed below.

Deep Vein Thrombosis Prophylaxis in Pediatric Neurosurgical Patients

Incidence of DVT in Pediatric Populations

The incidence of DVT in the hospitalized pediatric population is exceedingly low but on the rise; it approaches 0.2% in North America. As stays in the intensive care unit are prolonged with indwelling central venous catheters, the incidence of associated DVT naturally increases.

Recommendations

As the baseline rate of VTE is so low in children, level III guidelines recommend screening only the children who are symptomatic or have multiple proven risk fac-
tors of VTE (e.g., prolonged immobility, underlying malignancy, sepsis, protracted length of indwelling central venous access) and not to treat with any postoperative chemical prophylaxis unless the child has a history of VTE.

Deep Vein Thrombosis Prophylaxis in Vascular Neurosurgery Patients: The External Ventricular Drain

For the purposes of this discussion, neurovascular patients are those who have sustained spontaneous intracranial hemorrhage (subarachnoid, intraventricular hemorrhage, or intraparenchymal hemorrhage) from a vascular malformation (e.g., aneurysm, arteriovenous malformation, dural arteriovenous fistula, cavernous malformation). DVT prophylaxis in this subgroup of neurosurgical patients is usually not recommended until the source of hemorrhage is secured (i.e., by coiling, clipping, or resection). After the source is secured, these patients can generally be treated in a manner similar to the typical postcranial neurosurgical patient unless they need to have an external ventricular drain (EVD) placed or removed.

The EVDs are typically inserted either at the bedside in the intensive care unit or in the operating room. Their insertion is associated with a hemorrhage rate of 5 to 41%,37–41 with only a 0.5 to 2% risk of the hemorrhages becoming symptomatic. EVDs are often inserted before the definitive surgery to secure the source of hemorrhage; thus, their insertion contributes little to the algorithm of when to start chemical DVT prophylaxis. New symptomatic hemorrhage from EVD removal has been reported, however, in patients on subcutaneous LMWH and aspirin after coiling of a ruptured aneurysm.41 Although this was a report of a small number of patients, it suggested that there was an increased risk with either insertion or removal of an EVD within 24 hours of a patient receiving subcutaneous DVT prophylaxis. There is, however, considerable evidence to the contrary. Hoh et al39 reported a 9.2% EVD-associated hemorrhage rate even when a patient received full-systemic therapeutic anticoagulation with heparin during endovascular coiling of a ruptured aneurysm within 24 hours after ventriculostomy placement. Of these hemorrhages, only one patient (0.8%) was symptomatic. If the activated partial thromboplastin time was kept below 90, there was a 0% incidence of EVD-related hemorrhage from full systemic heparinization in their series. Thus, if a patient can tolerate a partial thromboplastin time up to 90 without increased hemorrhage rate within 24 hours, it can reasonably be concluded that starting UFH or LMWH for DVT prophylaxis 24 hours after an EVD placement would likely not result in an increased rate of statistically significant ICH. On the opposite end of the spectrum are patients receiving dual antiplatelet therapies after stent-assisted coiling. These patients suffered a 32% EVD hemorrhage rate, with a quarter of these hemorrhages becoming symptomatic.42 Thus, if a patient with an EVD is on dual antiplatelet therapy for a stent, subcutaneous DVT prophylaxis can be justifiably withheld.

Inferior Vena Cava Filters in Neurosurgical Patients

Theoretically, IVC filters are inserted to prevent pulmonary embolism; however, the insertion of these devices is not without risk. Complications include insertion-site hematoma (1%), IVC thrombosis that is often asymptomatic (up to 18%),43 post-thrombotic syndrome (7–40%), migration into the superior vena cava or right atria
(2–3%), and even erosion through the wall of the IVC into the duodenum or renal collecting system.\textsuperscript{43,44} Permanent IVC filters seem to lose their initial benefit in preventing PE and actually increase the morbidity of long-term recurrence of DVTs. With these safety concerns, retrievable filters have been developed to take advantage of short-term PE prevention benefit without the long-term disadvantages in patients with temporary contraindications to anticoagulation.\textsuperscript{44} Placing a retrievable filter in a patient requires a system to ensure the patient is not lost to follow-up, as the chances of removing the filter diminish exponentially after 6 weeks in most cases.

\begin{center}
\textbf{IVC Filters in Neurosurgery Patients}
\end{center}

Retrievable IVC filters are routinely used in two unique situations in neurosurgery patients. The first, in which there is clear benefit, is in a neurosurgery patient with a newly diagnosed DVT who is unable to receive systemic anticoagulation because of the risk of bleeding. Absolute contraindication to systemic anticoagulation is somewhat controversial but certainly includes recent (< 48 hours) intracranial or spinal surgery, ongoing gastrointestinal bleeding, severe thrombocytopenia, severe uncontrolled hypertension, or a known bleeding diathesis. IVC filters should be placed as soon as possible in these patients to prevent pulmonary embolus.

The second use, which remains controversial, is a prophylactic usage in patients with absolute contraindications to subcutaneous DVT prophylaxis who are at high risk for VTE. The two types of neurosurgical patients that may meet this definition are those with multiple DVT risk factors preparing to undergo a complex spinal reconstruction and those with acute multisystem neurotrauma/trauma. Both of these situations are discussed below.

\begin{center}
\textbf{IVC Filters as Prophylaxis in the Adult Spine Reconstruction Patient}
\end{center}

Major adult spinal reconstruction is regarded as a contraindication to anticoagulation; however, reconstructive spine surgery is a recognized risk factor for VTE.\textsuperscript{45–48} Rosner et al\textsuperscript{48} performed a pilot study of 22 patients and found decreased mortality and VTE rate in patients receiving a preoperative IVC filter for major spinal reconstruction. McClendon et al\textsuperscript{46} followed this pilot study with a large 219-patient study in high-risk patients undergoing adult spinal reconstruction. The definition of “high risk” included any of the following: history of DVT or PE, concurrent malignancy, hypercoagulability, prolonged immobilization (bedridden > 2 weeks before surgery), staged procedures of longer than five segment levels, combined anterior–posterior approaches, iliocaval manipulation during exposure, or planned anesthetic time of more than 8 hours. Venous lower extremity surveillance duplex Doppler ultrasonography was performed on all patients in the early postoperative period and then weekly. The lower extremity DVT rate was 18.7% (41/219 patients). The documented PE rate was 3.7% (8/219 patients) as measured by computed tomography (CT) angiography. The incidence of developing VTE (whether DVT or PE) was significantly higher in patients with anesthesia over 8 hours. Comparing the DVT-to-PE conversion rate in filtered versus nonfiltered historical controls with the same high-risk criteria resulted in a statistically significant decrease in rate of PE, with an odds ratio of 3.7.\textsuperscript{47}
Venous Thromboembolism (DVT and PE): Prophylaxis

IVC Filters as Prophylaxis in the Neurotrauma/Polytrauma Patient

Pulmonary embolism is often a preventable cause of late morbidity and mortality after trauma, as it occurs in up to 1.5 to 9% of patients who survive their initial trauma.44 In high-risk injury patterns, including severe closed head injury and spinal cord injury with paraplegia or quadriplegia prophylactically, IVC filters carry a level III evidence of recommendation for prophylactic use.49 In a large meta-analysis in which over half the included studies had sample sizes greater than 100 patients, the use of IVC filters in these predetermined trauma patients definitively decreased PE (0–9%) and PE-related death (0–0.8%) compared with historical controls.

Recommendations for IVC Filters in Neurosurgery Patients

Inferior vena cava filters should be used in any patient with a known DVT who is unable to undergo systemic anticoagulation for prevention of PE. IVC filters should be strongly considered for PE prophylaxis in TBI and SCI patients without DVT who are unable to receive subcutaneous DVT prophylaxis. Additionally, high-risk patients (those with previous history of DVT or PE, concurrent malignancy, hypercoagulability, or prolonged immobilization) preparing to undergo complex spine reconstruction, particularly if the general anesthetic time will be more than 8 hours, should be considered for a prophylactic filter as well.

KEY POINTS

- The incidence of deep venous thrombosis in the neurosurgical population varies with screening methods but averages 25% with mechanical prophylaxis alone. With the addition of subcutaneous chemoprophylaxis, the incidence drops to 15%.
- Chemical prophylaxis must be judged on a case-by-case basis, but starting treatment with subcutaneous heparin 24 to 48 hours after surgery is supported in the literature. Patients with underlying malignancy, prolonged immobility, or with a surgery lasting > 6 hours should be treated aggressively.
- Chemical deep venous thrombosis prophylaxis should not be started preoperatively in any cranial or spinal patient because of the significantly increased risk of bleeding. If a patient is on deep venous thrombosis prophylaxis already, it should be withheld 24 hours before the operation.
- Patients with traumatic brain or spinal cord injuries are an increased risk for venous thromboembolism. Deep venous thrombosis prophylaxis should be administered within 72 hours of admission with unfractionated heparin every 8 hours in patients with traumatic brain injury. For patients with spinal cord injury, low molecular weight heparin every 12 hours should be prescribed. If other high-risk features are present, a temporary inferior vena cava filter should strongly be considered.
- External ventricular drains are associated with a high rate of hemorrhagic complications at the time of insertion; however, there is no evidence to suggest deep venous thrombosis prophylaxis cannot safely be initiated 12 to 24 hours after insertion.
• Filters should be used as pulmonary embolism prevention in neurosurgical patients with known deep venous thrombosis and a contraindication to systemic anticoagulation. They should be considered as pulmonary embolism prophylaxis in high-risk patients without deep venous thrombosis who will undergo neurosurgery that will last > 6 hours.

**REVIEW QUESTIONS**

1. Risk factors for VTEs include:
   A. Operative duration < 60 minutes
   B. Hypercoagulability
   C. Malignant tumor
   D. Protein C or S deficiency
   E. Spinal cord injury with paralysis

2. True or false?
   A. Mechanical calf compression is a first-line method of prophylaxis for VTE.
   B. Mechanical calf compression carries a 5% risk of intracerebral hemorrhage.
   C. Chemical prophylaxis used postoperatively carries up to a 3% risk of intracerebral hemorrhage.
   D. LMWH is the chemical VTE prophylaxis agent of choice for all neurosurgery patients.
   E. Chemical prophylaxis is more efficacious when started preoperatively.

3. True or false?
   A. Low-dose UFH is typically started 24 hours postoperatively.
   B. Low-dose UFH is typically started intraoperatively.
   C. LMWH has a lower risk of intracerebral hemorrhage than low-dose UFH.
   D. Mechanical prophylaxis is usually started intraoperatively.
   E. Low-dose UFH reduces the risk of DVT by 40%.

4. True or false?
   A. The incidence of DVT in moderate to severe traumatic brain injury (TBI) as high as 33%.
   B. Use of LMWH with 24 hours of a craniotomy for TBI has an intracranial bleeding rate of 25%.
   C. Withholding chemoprophylaxis for longer than 48 hours after TBI results in a fivefold increase in the rate of DVT.
   D. IVC filters may provide protection from PE in high-risk patients.
   E. Patients with moderate to severe TBI should be screened with weekly Doppler ultrasonography for DVT even in receiving chemoprophylaxis.

5. True or false?
   A. Patients with spinal cord injury (SCI) have the highest rate for VTE of any neurosurgical condition.
   B. The highest risk for VTE in patients with SCI is in the first 12 hours after the trauma.
   C. VTE accounts for 5% of all deaths in the first year after SCI.
D. The risk of DVT increases 10-fold if chemical prophylaxis is delayed longer than 72 hours after SCI.
E. VTE prophylaxis for patients with SCI should be accomplished with LMWH and continued for a minimum of 12 weeks.

6. True or false?
   A. The incidence of DVT in pediatric hospitalized patients is ~ 0.2% in North America.
   B. Insertion of an external ventricular drain has a symptomatic hemorrhage risk of 2%.
   C. Patients with external ventricular drains can safely receive chemical prophylaxis (low-dose UFH or LMWH).
   D. External ventricular drains can be safely removed while patients are receiving chemical prophylaxis (low-dose UFH or LMWH).
   E. IVC filters have a < 3% risk of serious complications.

References

### ANSWER KEY

1. B, C, D, and E

2. A: True; B: False; C: True; D: False; E: False

3. A: True; B: False; C: False; D: True; E: True

4. A: True; B: False; C: True; D: True; E: True

5. A: True; B: False; C: False; D: True; E: True

6. A: True; B: True; C: True; D: False; E: False
Arterial and venous thrombotic events combined, which include acute coronary syndromes, stroke, peripheral arterial thrombosis, deep venous thrombosis, and pulmonary embolism, are likely responsible for more morbidity and mortality than any other condition in the developed world. A common feature of the management of all thromboembolic vascular diseases is the use of antithrombotic agents. These agents, which include antiplatelet drugs, anticoagulants, and thrombolytic agents, are used to prevent thrombotic events, prevent or mitigate the complications of thrombotic events, and restore vascular patency to prevent loss of tissue, organ, and limb function. Although lifesaving for many patients, these antithrombotic therapies present unique challenges for managing patients with neurosurgical problems taking antithrombotic medications. In particular, the management of neurosurgical patients taking antiplatelet agents for coronary artery disease or on anticoagulation protocols for atrial fibrillation or mechanical heart valves presents complex risk/benefit dilemmas. Further, the introduction of novel oral anticoagulants into clinical use during the past few years adds additional complexity.

Cardiovascular Disease and Antiplatelet Agents

An estimated 40% of United States adults take an antiplatelet agent for the prevention of cardiovascular or cerebrovascular disease. Multiple studies have demonstrated the benefits of antiplatelet agents in preventing cardiovascular disease. Patients on primary prophylaxis (no known cardiovascular disease), on secondary prophylaxis (known cardiovascular disease), or who have a cardiac stent have inherently different risks associated with temporary cessation of antiplatelet therapy. Studies have shown that in the setting of primary prophylaxis, antiplatelet drugs provide benefits against myocardial infarction in men and stroke in women, but are associated with increased risks (e.g., ulcers/gastrointestinal bleeding and hemorrhagic strokes). Because of these known risks, antiplatelet drugs are recommended for primary prophylaxis only for patients with a demonstrable increase in cardiovascular risk. The United States Preventative Task Force recommends the use of aspirin to reduce myocardial infarction in men (45–80 years old) and stroke in women (55–80 years old) when the potential benefit in each group outweighs the risk of gastrointestinal hemorrhage. In contrast, studies on secondary prophylaxis show that antiplatelet drugs are superior to anticoagulation medications for recurrent myocardial infarction and superior to placebo for the prevention of myocardial infarction, sudden death, and the progression of coronary artery disease in patients with stable angina. Although patients appropriately prescribed antiplatelet therapy for
primary or secondary prevention of cardiovascular disease gain net benefit, the benefits are small enough that when faced with a surgery with high bleeding risk, such as most neurosurgical procedures, cautious perioperative management is warranted.

Because the risk of thrombotic complication is low, the perioperative recommendation for patients prescribed an antiplatelet agent for primary prophylaxis is to stop antiplatelet medications 5 to 7 days before surgery and resume them once the postoperative window for increased hemorrhage is closed. In contrast, one meta-analysis showed that if patients on aspirin for secondary prophylaxis routinely stopped taking it for surgery, they were at a significantly increased risk for cardiovascular events. This risk must be weighed against evidence that concurrent aspirin use can cause a 50% increase in significant hemorrhage during the perioperative period, which is particularly problematic for the neurosurgical patient. Therefore, the perioperative recommendation for patients taking antiplatelet drugs for secondary prophylaxis in the setting of a surgery with high bleeding risk is drug cessation 5 to 7 days before surgery and resumption 24 hours after surgery (or whenever the surgeon deems the risk of hemorrhage in the particular patient to be low enough). If a patient is taking antiplatelet medication and urgent or emergent surgery is required, then the 2012 American College of Chest Physicians (ACCP) recommendation is to “transfuse platelets or other hemostatic agents” to try to prevent excessive intraoperative bleeding.

**Patients with Coronary Stents**

The most difficult clinical scenario encountered by neurosurgeons relating to antithrombotic medications is when patients with recently placed cardiac stents or recent acute myocardial infarction need neurosurgical interventions. With more than 6 million patients having cardiac stents and 5% of these patients needing surgery within 1 year of stent placement, all surgeons must know the risk of antiplatelet cessation in these patients to better educate patients and their families about the high risks involved. A prothrombotic milieu, which lasts 1.5 to 3 months with bare metal stents and 12 months in drug-eluting stents, is created after stent placement, and dual antiplatelet therapy (concomitant aspirin and thienopyridine) significantly reduces the risk of cardiovascular events when compared with aspirin alone. Furthermore, because of a high risk of recurrent ischemia, 1 year of dual antiplatelet therapy is also recommended for patients who do not receive a cardiac stent after acute coronary syndrome or myocardial infarction.

The statistics behind the risk of antiplatelet cessation in patients with recently placed stents are alarming: antiplatelet drug cessation increases the cardiac complication rate with an odds ratio of 89.8. Furthermore, the most significant independent risk factor for stent thrombosis is premature antiplatelet cessation (odds ratio 14–57), and 30 to 40% of the instances of antiplatelet cessation were for surgery. The adverse cardiac event rate in patients undergoing surgery who temporarily cease antiplatelet therapy is more than double if this occurs < 30 days after stent placement than if patients are > 90 days from stent placement. More sobering evidence is provided by studies that showed that interruption of dual antiplatelet therapy in the first month after placement of a stent for noncardiac surgery led to a cardiac mortality rate of 86%, whereas the mortality rate was just 5% in patients who maintained dual antiplatelet therapy, and that with drug-eluting stents, the stent thrombosis rate was 31% in patients who stopped taking thieno-
pyridine and clopidogrel and 0% in patients who did not stop. Yet, when dual antiplatelet therapy is continued through the perioperative period, the relative bleeding risk is increased 50% when compared with use of aspirin alone, and there is an increase in blood transfusion requirements.

Because of this very complex risk/benefit situation, the perioperative management of the neurosurgical patient with a cardiac stent should be done systematically with three main considerations. First, the patient’s cardiologist should be involved in management decisions. Second, surgery should be delayed, if possible, until the very high prothrombotic state after stent implantation is lessened: 1 year for patients with a drug-eluting stent and 3 months for those with a bare metal stent. Third, aspirin therapy should be maintained whenever possible in these patients who are at a high risk for a perioperative cardiovascular event unless the bleeding risk of the surgery prohibits doing so. Case example 1 provides a clinical scenario that highlights the difficulty of managing a patient with traumatic intracranial hemorrhage and recent placement of cardiac stents.

### Case Example 1

An 83-year-old man with a past medical history of coronary disease with previous multivessel coronary artery bypass grafting, diabetes, hypertension, and prostate cancer presented with a non–ST-segment elevation myocardial infarction (non-STEMI) and had three drug-eluting stents placed as treatment. After the procedure, he fell and became slightly confused (not oriented to location), but had a Glasgow Coma Scale score of 14 and was otherwise neurologically intact. A computed tomography (CT) scan showed a 1-cm left acute subdural hematoma with 5 mm of midline shift (Fig. 12.1a). He also suffered a right humeral head fracture as result of his fall (Fig. 12.1b). After the patient was transferred from the medical intensive care unit to the neurological intensive care unit, a repeat CT scan was stable. The patient’s aspirin therapy regimen was continued, but clopidogrel was discontinued in case he suffered a neurologic decline and needed urgent subdural hematoma evacuation. Although the patient was monitored with serial electrocardiograms every 8 hours because of the high risk of stent thrombosis, he developed chest pain, and a subsequent echocardiogram demonstrated a new wall motion abnormality consistent with myocardial infarction from stent thrombosis. Serial CT scans every 3 to 4 days showed the subdural hematoma was stable (Fig. 12.1c). After the patient had developed a slight facial droop on hospital day 7, another CT scan showed the patient had suffered a left subacute posterior inferior cerebellar artery stroke (Fig. 12.1d). On hospital day 13, the patient had an open reduction and internal fixation of his right humerus but suffered a massive STEMI and did not survive.

### Management of Patients

A recent survey of interventional cardiologists further demonstrates the complexity and uncertainty in managing these patients. Forty-eight percent of respondents said that if their patient required surgery, they would find a surgeon who would be willing to operate while the patient continued taking dual antiplatelet therapy. On the other hand, 50% said they would use an intravenous platelet glycoprotein IIb/IIIa inhibitor as a bridge during the perioperative period (although there is no controlled evidence to support this practice, especially in intracranial surgery pa-
patients who are at high risk for hemorrhage). When asked about patients who had drug-eluting stents for more than 1 year but needed surgery, 48% of interventional cardiologists still said aspirin therapy should be continued, 41% said dual antiplatelet therapy was necessary, and only 11% said they could be stopped. The ultimate decision in these situations needs to be made by the surgeon as part of a multidisciplinary approach with the cardiologists and thrombosis specialists, and the patient and family must be made aware of the high risks associated with each approach. Fig. 12.2 provides a summary of perioperative antiplatelet management considerations in these patients.

**Anticoagulant Therapy in Patients with Atrial Fibrillation**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is the underlying cause of 100,000 strokes annually in the United States. Furthermore, AF-related strokes result in a 25% mortality rate and 35% severe disability rate in survivors. Because AF is so common and has an increased risk of stroke, it is the most common indication for anticoagulation with vitamin K antagonists (VKA); 1 million people in the United States take warfarin for AF each year, and by 2050 the worldwide estimated use will increase from 6 million to 10 million people.

**Fig. 12.1a–d** Case example 1. (a) Initial head computed tomography (CT) showing 1-cm left acute subdural hematoma with 5-mm midline shift. (b) Right anteroposterior shoulder radiograph demonstrating humeral head fracture. (c) CT scan from several days after initial trauma showing stable evolution of acute subdural hematoma. (d) Head CT showing subacute left posterior inferior cerebellar artery stroke on hospital day 7 after patient developed facial droop.
Atrial fibrillation has been shown to be an independent risk factor for mortality because it increases the risk of stroke, negatively affects the heart, can worsen heart failure, and can lead to increased mortality in patients with myocardial infarction. The overall annual risk of stroke for all AF patients without antithrombotic drugs is 5%. Importantly, the annual risk of stroke for AF patients is not the same for all patients—a consideration that has important implications for perioperative management. An individual patient's stroke risk can be estimated based on the number of associated clinical risk factors. A commonly used risk stratification scheme, the CHADS2 score, is shown in Table 12.1. By applying the CHADS2 score, patients can be categorized as high, medium, and low risk for stroke (annual stroke risks of < 4%, 4–10%, and > 10%, respectively). Most patients with AF should be prescribed an antithrombotic medication to reduce the risk of stroke. Warfarin

Table 12.1 CHADS2 Atrial Fibrillation Stroke Risk Stratification

<table>
<thead>
<tr>
<th>Points</th>
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<tbody>
<tr>
<td>C = congestive heart failure</td>
</tr>
<tr>
<td>H = hypertension</td>
</tr>
<tr>
<td>A = age ≥ 75 years</td>
</tr>
<tr>
<td>D = diabetes</td>
</tr>
<tr>
<td>S2 = stroke/transient ischemic attack</td>
</tr>
</tbody>
</table>

Note: Patients with scores of 0 have an annual risk of stroke of < 2%. Those with scores of ≥ 3 have an annual risk of stroke > 5% per year.
is the preferred agent for most patients because it reduces the risk of stroke by > 60%; however, aspirin, or the combination of aspirin and clopidogrel, is appropriate for some patients.

In preparation for surgical procedures, patients (i.e., all patients except those undergoing a procedure with a low risk of bleeding) must not be taking an anticoagulant because of the risk of excessive intraoperative bleeding. Thus, physicians must provide guidance as to when the use of warfarin should be stopped preoperatively, if a short-acting bridging anticoagulant (e.g., heparin or low molecular weight heparin (LMWH)) is necessary during the period of warfarin cessation, and when warfarin use should be resumed postoperatively. Simple math would suggest that because the overall stroke risk for all AF patients is 5% annually, then an 8-day perioperative period of warfarin cessation would have a risk of 0.013% daily or ~ 0.1% for 8 days. Yet, the observed risk of stroke/transient ischemic attack (TIA) for all AF surgical patients who have not received bridging prophylaxis may be 1% or greater. This higher than expected risk of stroke may be due to the fact that surgical patients are predisposed to thromboembolic events in the immediate postoperative period regardless of their anticoagulation status. One large study of 700 AF patients undergoing elective surgery showed an overall thromboembolic event rate of 0.6% when bridging was used in only 2.5% of patients.

From a practical perspective, management should be individualized to the patient’s estimated risk of stroke and the bleeding risk of the surgical procedure. For low-risk AF patients (e.g., those with a CHADS<sub>2</sub> score ≤ 2), bridging therapy is not necessary. In these patients, warfarin therapy should be stopped 5 to 6 days before surgery, and the international normalized ratio (INR) should be checked 24 hours before surgery to determine whether any reversal agents are necessary. If the INR is not at the goal of < 1.3, then 2.5 mg of oral vitamin K should be administered to ensure that the INR is at the goal the morning of surgery. In patients at moderate or high risk of AF (e.g., those with a CHADS<sub>2</sub> score of 3–4 and 5–6, respectively; patients with a recent cerebrovascular accident [CVA]/TIA or rheumatic valvular heart disease are also high risk), warfarin should be stopped 5 to 6 days preoperatively, and the decision to use bridging therapy with heparin or LMWH must be made on a case-by-case basis. For most patients, bridging therapy can be used safely in the preoperative period but should be used cautiously in the postoperative setting in which bleeding risk is heightened; the risk of severe hemorrhage after major surgery can be as high as 20% when full-dose bridging is used.

The 2012 ACCP recommendations favor LMWH over a heparin infusion as a bridge therapy because the costs are equivalent and LMWH has demonstrated noninferiority, is much easier to administer, and does not require laboratory monitoring. If LMWH is used, then the last dose should be half of the daily dose given > 24 hours before surgery. If intravenous heparin is used, it should be stopped 4 to 6 hours before surgery. The timing of postoperative resumption of anticoagulants must be determined by the surgeon and be based on the patient’s individual risk level. The postoperative hemorrhage rate for all surgery types is doubled when prophylactic doses of heparin are begun at 4 to 8 hours rather than 12 to 24 hours postoperatively. Furthermore, if therapeutic heparin is resumed within 24 hours of surgery, the odds ratio for major hemorrhage is 4.8, and the major hemorrhage rate after resumption of therapeutic heparin after major surgery is 10 to 20%. The risk of postoperative hemorrhage also increases with increasing patient age. When patients are at a high risk for hemorrhage postoperatively, it is recommended to wait at least 48 to 72 hours to resume therapeutic anticoagulation or
to use low dosages or avoid parenteral anticoagulation entirely.\textsuperscript{4,6} Once again, the decision must be made on a case-by-case basis by evaluating the patient’s probability of hemorrhage and the risk of thromboembolic event.\textsuperscript{4} Table 12.2 summarizes a perioperative approach to the patient on long-term anticoagulant therapy.

Anticoagulant Therapy in Patients with Mechanical Heart Valves

Heart valve replacement surgery has been a lifesaving intervention for 50,000 to 100,000 patients a year for over 50 years, with > 80 different heart valve models used since 1950 (http://emedicine.medscape.com/article/780702-overview). Heart valve replacement is one of the most common indications for anticoagulation therapy to prevent the risk of CVA and other systemic thromboembolic conditions.

Perioperative Management

The management of the duration and timing of the cessation of anticoagulation therapy in the perioperative setting in patients with mechanical heart valves undergoing additional surgery is similar to the strategy used for AF patients with respect to the need for stratification based on risk (Table 12.2).\textsuperscript{4,6} Low-risk patients include those who have a bi-leaflet aortic valve prosthesis without AF and have no other risk factors for stroke such as prior CVA/TIA, hypertension, diabetes mellitus, congestive heart failure, or age > 75 years. These patients probably do not need bridging therapy, but low-dose subcutaneous LMWH could be used if bridging therapy was desired.\textsuperscript{4,6} Moderate-risk patients are those who have a bi-leaflet aortic valve prosthesis but also have one of the risk factors for CVA.\textsuperscript{4,6} Recommendations for this group are the same as those for moderate-risk AF patients with a CHADS\textsubscript{2} score of 3 to 4; decisions on anticoagulation therapy must be made on an individual basis. The risk of potential hemorrhage after major surgery is as high as 10 to 20\% in patients who restart therapeutic heparin within 24 hours, which has led to the official recommendation that therapeutic anticoagulation be delayed at least 48 to 72 hours (if it is resumed at all).\textsuperscript{6} The same recommendations hold true for high-risk heart valve patients (those with any mitral valve prosthesis or an older type of aortic valve prosthesis [e.g., tilting disk or caged-ball] and those with a recent CVA/TIA).\textsuperscript{6} If the decision to use bridging therapy is made, then the same drug choice, timing, and dosing parameters used for AF patients apply as discussed earlier in the AF section.\textsuperscript{6}

The Emergence of New Pharmacological Antithrombotic Agents

The complexity of managing surgical patients taking antithrombotic medications has become much more difficult because of the development of newer anticoagulant and antiplatelet drugs that can be more potent and generally lack an antidote. An exhaustive description of the agents is beyond the scope of this chapter, but it is vital that practicing surgeons and critical care physicians know the basics about their indications, effectiveness, and reversibility. Major bleeding occurs annually
### Table 12.2 General Recommendations for Managing Warfarin in the Perioperative Period for Major Neurosurgical Procedures

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Indication for VKA</th>
<th>Mechanical Valve</th>
<th>Atrial Fibrillation</th>
<th>Bridging Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitral</td>
<td>CHADS$_2$ score = 5–6</td>
<td>Stop warfarin 5 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Older generation</td>
<td>Stroke/TIA past 3 months; rheumatic valve disease</td>
<td>Start heparin or LMWH 3 days prior (last dose of LMWH 24 hours prior to surgery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recent stroke/TIA</td>
<td></td>
<td>LMWH or UFH should not be resumed at a fixed time after a surgery or procedure without consideration of the anticipated bleeding risk or adequacy of postoperative hemostasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If therapeutic-dose bridging is used in patients at high risk for postoperative bleeding, its initiation should be delayed for 48 to 72 hours after surgery when adequate surgical hemostasis has been achieved; if bleeding risk continues beyond 72 hours, options include a low-dose heparin bridging regimen or VKA resumption alone without postoperative bridging</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>Bi-leaflet aortic valve</td>
<td>CHADS$_2$ score = 3–4</td>
<td>Stop warfarin 5 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke risk factors</td>
<td></td>
<td>Start heparin or LMWH 3 days prior (last dose of LMWH 24 hours prior to surgery)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LMWH or UFH should not be resumed at a fixed time after a surgery or procedure without consideration of the anticipated bleeding risk or adequacy of postoperative hemostasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If therapeutic-dose bridging is used in patients at high risk for postoperative bleeding, its initiation should be delayed for 48 to 72 hours after surgery when adequate surgical hemostasis has been achieved; if bleeding risk continues beyond 72 hours, options include a low-dose heparin bridging regimen or VKA resumption alone without postoperative bridging</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>Bi-leaflet aortic valve</td>
<td>CHADS$_2$ score = 0–2</td>
<td>No bridging required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No stroke risk factors</td>
<td>No prior stroke/TIA</td>
<td>Stop warfarin 5 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Resume after surgery when hemostasis achieved</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, low molecular weight heparin; TIA, transient ischemic attack; UFH, unfractionated heparin; VKA, vitamin K antagonist
in 1 to 2% of patients taking warfarin, including 3,500 cases of intracranial hemorrhage, and warfarin causes more deaths from adverse drug-related events each year than any other medication. The newer anticoagulant therapies have been developed to improve upon the many limitations of warfarin; they act faster to eliminate the need for bridging therapy, they have a more reliable and predictable anticoagulant effect to eliminate the frequent INR checks required with warfarin use, they possess a lower potential for negative dietary and other medication interactions, and they are specifically targeted to a further downfield coagulation enzyme to avoid adverse effects. Of emerging anticoagulants, the oral direct thrombin inhibitors and factor-Xa inhibitors have already been introduced into clinical use.

**Direct Thrombin Inhibitors**

Dabigatran etexilate is an oral direct thrombin inhibitor whose effect peaks at 2 hours. Its half-life of 17 hours after steady-state levels allows once-daily dosing for some patients (although it is predominantly excreted by the kidneys and is thus contraindicated in patients with renal failure). It inhibits free and fibrin-bound thrombin, whereas heparin and LMWH cannot inhibit the fibrin-bound form. In addition to addressing many of the pharmacological weaknesses of warfarin, multiple randomized controlled trials have shown that it is superior or equivalent to warfarin in reducing major bleeding events, thromboembolic deaths after orthopedic joint replacements, symptomatic venous thromboembolic events, and thromboembolic deaths in newly diagnosed acute venous thrombus patients. It also results in superior outcomes with lower rates of CVA/systemic embolism, intracranial hemorrhage, major bleeding, and overall complications in AF patients.

Although the benefits of easier dosing and improved efficacy have led to large numbers of patients switching to dabigatran, the risk of major bleeding or clinically relevant but nonmajor bleeding is still 1.3 to 5.3%. The most serious concern, however, is that, unlike warfarin, there is no reversal agent, and giving clotting factors is unlikely to help because the drug does not target the factors replenished with transfusion. This has led to catastrophic fatal intracranial hemorrhages evolving from minor traumatic hemorrhages with no efficacious antidote. Hemodialysis is expected to remove 35 to 60% of the drug after 2 to 3 hours, but this may be insufficient because of the rapid progression of bleeding. Furthermore, laboratory monitoring is problematic because laboratory tests such as the activated partial thromboplastin time (aPTT) and INR are not reliable in assessing the degree of anticoagulant effect. The thrombin time and the ecarin clotting time are better diagnostic tests to monitor the level of anticoagulation of dabigatran, but these tests are not widely available.

When patients taking dabigatran need to undergo high-risk procedures such as intracranial surgery, the drug cessation time can be as short as 2 days in patients with good kidney function. This should be confirmed with the thrombin time and ecarin clotting time tests because of the risk of hemorrhage if the effects of anticoagulation therapy have not yet worn off. If these tests are not available, then a completely normal aPTT suggests little residual anticoagulant effect. Dabigatran may be resumed 48 to 72 hours after surgery, but the delay should be longer if there is a concern about poor intraoperative hemostasis or if the surgical procedure is thought to have a high bleeding risk—especially given the difficulty in managing dabigatran-related bleeding complications.
Direct Factor Xa Inhibitors

Oral factor Xa inhibitors (e.g., rivaroxaban and apixaban) act by reversibly blocking the active site of factor Xa, thus inhibiting factor Xa’s activation of thrombin.\(^{23}\) Apixaban is taken orally, has a half-life of 12 hours, and is excreted renally (25%) and cleared fecally.\(^{23}\) In a large study of patients undergoing knee replacement surgery, apixaban was shown to be superior to LMWH and warfarin with respect to total venous thromboembolism and all-cause mortality.\(^{30}\) Apixaban has also been shown to be superior to aspirin in AF patients who cannot tolerate vitamin K antagonists, with no major difference in hemorrhage rates, including intracranial hemorrhage rates.\(^{31}\) Rivaroxaban has a half-life of 9 hours and is similar to apixaban in that it is cleared renally and through the gastrointestinal tract.\(^{23}\) In a large study of > 2,500 patients undergoing knee replacement, oral rivaroxaban was shown to be superior to subcutaneous LMWH for deep venous thrombosis, nonfatal pulmonary embolism, and all-cause mortality.\(^{23,32}\) Rivaroxaban has also been shown to be noninferior to LMWH and VKA in the treatment of deep venous thrombosis/pulmonary embolism patients\(^{33}\) and noninferior to warfarin in the treatment of AF with the end point of stroke or non–central nervous system systemic embolism.\(^{34}\)

As of December 2012, rivaroxaban has been approved by the Food and Drug Administration for use in the United States for prevention of venous thromboembolism in orthopedic surgery patients, stroke prevention in patients with AF, and treatment of patients with venous thromboembolism. As in the oral direct thrombin inhibitors, there is no recognized antidote to reverse the effects of the oral factor Xa inhibitors. Additionally, currently available laboratory tests are not reliable in assessing the degree of anticoagulation in patients taking a factor Xa inhibitor. For these reasons, caution must be exercised when using these agents in the perioperative setting. The recommendations for rivaroxaban and apixaban use are similar to those for dabigatran use, with patients skipping two doses preoperatively (three to four doses if a patient taking rivaroxaban has poor renal function).\(^{29}\) Postoperatively, patients could resume their anticoagulation therapy 48 to 72 hours after surgery if there is no concern for poor hemostasis and if there is no need for further procedures or removal of drains (e.g., external ventricular drain, epidural catheter).\(^{29}\)

P2Y12 Antagonists

Prasugrel, a thienopyridine (P2Y12 receptor inhibitor [see Chapter 5]), is similar to clopidogrel in its mode of function, but it is more potent because it is more efficiently absorbed, with the maximum plasma concentration of its active metabolite reached at 30 minutes, and because there is not the high rate of genetic resistance with prasugrel that is commonly seen with clopidogrel.\(^{23,35}\) The active metabolite has a half-life of 7 hours (range 2–15 hours) (www.effient.com). Its popularity is increasing because it is twice as effective as clopidogrel in preventing stent thrombosis after percutaneous coronary intervention; it has been shown, however, to increase the nonsurgical hemorrhage rate by 32% when compared with clopidogrel, and has increased rates of intracranial hemorrhage when compared with clopidogrel.\(^{8,23,36}\) The rates of fatal and life-threatening bleeding were also increased with prasugrel when compared with clopidogrel, although the patients who had higher bleeding rates tended to have the same risk factors predisposing them to hemorrhage as in patients taking other antithrombotic drugs.\(^{23}\) General
perioperative management of antiplatelet medications for percutaneous coronary intervention was discussed previously. Prasugrel, like clopidogrel, has no antidote, and dialysis is most likely ineffective (http://www.scahq.org/newsLetter/newsletters/2010aug/DI%20Update.html and www.effient.com). The manufacturer’s recommendation is that the patient should have stopped taking prasugrel 7 days before surgery (www.effient.com). Platelet transfusions are the only recommended treatment, but the efficacy is not well defined. If surgery can be delayed 24 to 48 hours, this may provide time for the metabolism of prasugrel’s active metabolite (http://www.scahq.org/newsLetter/newsletters/2010aug/DI%20Update.html). Case example 2 provides an example of catastrophic intracranial hemorrhaging in a patient who had intracranial surgery while taking prasugrel.

Case Example 2

A 65-year-old man complained of nausea, headache, and dysarthria before going to bed and was unconscious a few hours later. He was taken to a hospital where he was intubated because of his low Glasgow Coma Scale score of 7). A head CT scan revealed a large left cerebellar hemorrhage (4 × 2 cm) with fourth ventricular effacement, obstructive hydrocephalus, downward tonsillar herniation, and uncal herniation (Fig. 12.3a,b). The patient had had cardiac stents placed 4 weeks prior

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**Fig. 12.3 a–d**  Case example 2. (a) Head CT showing a large left cerebellar hemorrhage. (b) Fourth ventricular effacement, obstructive hydrocephalus, downward tonsillar herniation, and uncal herniation as a result of the cerebellar hemorrhage. (c) Postoperative CT scan showing a large right frontal intraparenchymal and intraventricular hemorrhage associated with the EVD catheter pass while the patient was taking prasugrel. (d) Postoperative CT scan demonstrating reaccumulation of blood at the site of the cerebellar hemorrhage due to inability to achieve hemostasis while the patient was taking prasugrel.
to presentation after a heart attack 8 weeks before presentation and was taking warfarin and prasugrel. His INR was measured at 3.0 at the hospital, and a repeat INR at our institution was 1.7. The patient was given fresh frozen plasma and a platelet transfusion, and he was taken urgently to the operating room for placement of an external ventricular drain (EVD) followed by a cerebellar hemorrhage evacuation with decompression. The EVD was placed easily, but the patient developed a large subgaleal hematoma. The cerebellar hemorrhage and decompressive surgery was very difficult because all attempts at hemostasis were met with diffuse oozing that could not be controlled. Postoperative CT scan revealed the patient had a large right frontal intraparenchymal and intraventricular hemorrhage associated with the EVD catheter and a reaccumulation of blood at the site of his cerebellar hemorrhage (Fig. 12.3c,d). The patient’s family in discussion with his care team decided he should be given comfort care measures only, and he soon expired.

Conclusion

The use of antithrombotic therapies for patients with cardiac conditions such as coronary artery disease, AF, and mechanical heart valves is often lifesaving; however, the use of these agents presents unique management challenges in the perioperative setting because of the possibility of uncontrolled bleeding. There is no “one size fits all” approach to management. Rather, an understanding of an individual patient’s thrombotic risk, the bleeding risks associated with the planned procedure, and the unique pharmacological properties of the patient’s antithrombotic therapy is required to develop an individualized care plan to ensure the best possible outcomes.

KEY POINTS

• The perioperative recommendation for patients prescribed an antiplatelet agent for primary prophylaxis (no known cardiovascular disease) is to stop antiplatelet medications 5 to 7 days before surgery and resume them once the risk of postoperative hemorrhage has passed.
• The perioperative recommendation for patients prescribed an antiplatelet agent for secondary prophylaxis (known cardiovascular disease such as history of myocardial infarction or stable angina) is to stop antiplatelet medications 5 to 7 days before surgery and resume them at 24 hours postoperatively, but only at the surgeon’s discretion. The surgeon should believe that the risk of hemorrhage is low before the resumption of antiplatelet agents.
• Patients with coronary stents who require neurosurgery present a particularly complex risk/benefit analysis:
  ◦ An experienced cardiologist, preferably the patient’s own, should be involved in all management decisions.
  ◦ Neurosurgery should be delayed until the high-risk period for stent thrombosis has passed—1 year for drug-eluting stents and 3 months for bare metal stents.
  ◦ Aspirin should be continued through surgery if possible, as is often the case in spine surgery. If the risk of bleeding is high, as in cranial surgery,
then aspirin should be restarted as soon as possible at the surgeon’s discretion.

- The CHADS₂ score can be used to estimate the annual risk for stroke in a patient with atrial fibrillation:
  - Low-risk patients do not require anticoagulation bridging therapy. INR should return to < 1.3 preoperatively.
  - Moderate- or high-risk patients will likely require bridging therapy after calculation of their individual risk.
  - Postoperative bridging anticoagulation should resume as soon as the surgeon considers the period of high hemorrhage risk to have passed, generally after 48 to 72 hours (see Table 12.2).

- Patients with mechanical heart valve replacements can be stratified according to risk and managed along the same guidelines as patients with atrial fibrillation (see Table 12.2).

- The direct thrombin inhibitors, such as dabigatran, have no known antidotes. Therefore, these drugs should be stopped 2 to 3 days (or two doses) prior to neurosurgery, with the complete absence of anticoagulation effect proven by a totally normal aPTT or a normal thrombin time.

- The factor Xa inhibitors, such as rivaroxaban, also have no known antidotes. Unlike the direct thrombin inhibitors, though, there is no reliable laboratory test to assess the degree of anticoagulation effect. They should be used with great caution in the perioperative period. These drugs should be stopped two doses prior to neurosurgery and earlier in patients with poor renal clearance.

- The newer thienopyridines (P2Y₁₂ inhibitors) such as prasugrel should be stopped at least 7 days prior to surgery. The decision to stop these agents is made along the guidelines for management of patients with coronary stents. If surgery can be delayed safely for 24 to 48 hours, the active metabolite of prasugrel may be sufficiently metabolized in that time to improve platelet activity.

REVIEW QUESTIONS

1. A 58-year-old woman taking dabigatran for atrial fibrillation, with a past medical history significant for hypertension and diabetes, has a meningioma that has been growing and causing worsening headaches. She has decided to undergo craniotomy for meningioma resection. What should be done preoperatively with her dabigatran, and what bridging therapy, if any, is needed so that she is ready for her craniotomy for tumor resection?
   A. Stop dabigatran 7 days before craniotomy and bridge with LMWH until the day before surgery.
   B. Stop dabigatran 7 days before dabigatran and do not bridge with any medications before surgery.
   C. Stop dabigatran 2 days before craniotomy and bridge with LMWH 2 days prior to surgery.
   D. Stop dabigatran 2 days before craniotomy and do not bridge with any medications before surgery.
2. What diagnostic tests are the most reliable for assessing the level of anticoagulation for patients taking rivaroxaban or apixaban?
   A. PT/INR  
   B. PTT  
   C. Both  
   D. Neither

3. True or false: Patients who are taking dabigatran can undergo hemodialysis to have as much as 60% of the drug removed from the body in 3 hours.

4. The novel oral anticoagulants such as dabigatran and rivaroxaban were designed to improve on all of the following pharmacological limitations of warfarin except:
   A. A slower acting agent often necessitating bridging therapy while therapeutic levels are reached.  
   B. Unpredictable and unreliable anticoagulant effects necessitating frequent INR laboratory checking.  
   C. Difficult and time-consuming to reverse the anticoagulant effect.  
   D. Nonspecific upfield effects on coagulation enzyme cascade.

5. A 70-year-old man undergoes an emergency craniotomy for evacuation of an acute subdural hematoma after a motor vehicle accident. Which of the following scenarios would have the highest risk of a postoperative cardiac event the longer that antiplatelet agents are withheld?
   A. The patient recently had a drug-eluting stent placed 9 months prior and is prescribed dual antiplatelet therapy at home.  
   B. The patient had a drug-eluting stent placed 2 weeks prior and is prescribed dual antiplatelet therapy at home.  
   C. The patient had a bare metal stent placed 11 months prior and takes dual antiplatelet therapy at home.  
   D. The patient had a bare metal stent placed 4 months prior and takes dual antiplatelet therapy at home.

6. A 67-year-old man with a prosthetic mitral valve taking warfarin had a first-time grand-mal seizure and was found to have a right frontal lesion with imaging findings concerning for high-grade astrocytoma. His INR was 2.6 and he had a history of hypertension. Prior to craniotomy, when his warfarin therapy is stopped 7 days before craniotomy, what bridging therapy, if any, is needed?
   A. Bridge with LMWH with the last dose in the evening prior to surgery (12 hours before surgery).  
   B. Bridge with LMWH with the last dose the morning prior to surgery (24 hours prior to surgery).  
   C. Bridge with LMWH the last dose 2 days prior to surgery (24 to 48 hours before surgery).  
   D. Do not bridge with any medications before surgery.
References


**ANSWER KEY**

1. D  
2. D  
3. True  
4. C  
5. B  
6. B
Cerebral venous sinus thrombosis (CVST), or thrombosis of the intracranial veins and sinuses, is a rare disease with a variety of causes that accounts for 1% of all strokes. CVST is slightly more common in women due to pregnancy, the puerperium, and oral contraceptive use. Diagnosis is still frequently overlooked or delayed as a result of the wide spectrum of clinical symptoms and the often subacute onset. Because of its myriad causes and presentations, CVST is a disease that may be encountered by a wide variety of clinicians and specialties. Heparin is the treatment of choice. The prognosis is usually good, but adverse outcomes occur unpredictably and may lead to serious sequelae such as hemorrhage, brain herniation, or even death if not recognized and treated early.

History and Definitions

Cerebral venous sinus thrombosis is a rare type of cerebrovascular disease recognized as early as 150 years ago. Initial descriptions focused on CVST as an infectious disorder that commonly affected the superior sagittal sinus and resulted in bilateral or alternating focal deficits, seizures, and coma, often leading to death. CVST was commonly diagnosed almost exclusively at autopsy and therefore considered to always be lethal. In early angiographic series, mortality still ranged between 30% and 50%, but in several recent series using modern imaging techniques a more benign condition has emerged, with a mortality of less than 10%. Over the past 25 years, CVST has been diagnosed much more frequently due to greater awareness and the availability of advanced neuroimaging such as magnetic resonance imaging (MRI).

The venous territories of the brain are less well defined than the arterial territories due to the presence of extensive anastomoses between cortical veins. These allow the development of collateral circulation in the event of a venous occlusion. The main cerebral venous sinuses affected by CVST are the superior sagittal sinus (72%) and the lateral sinuses (70%). In about one third of cases more than one sinus is affected. In 30 to 40% of cases both sinuses and cerebral or cerebellar veins are involved.

Epidemiology

The exact incidence in adults is unknown but is certainly much higher than previously thought based on autopsy series. The incidence rate may be as high as 30 to 40 cases per million adults. A Canadian study reported an incidence of 0.67 cases
per 100,000 children younger than 18 years old; 43% of the cases reported in children were in neonates. The peak incidence in adults is in the third decade, with a male/female ratio of 3:10. This imbalance may be due to increased risk of CVST associated with pregnancy, the puerperium, and oral contraceptives/hormone therapies. This female preponderance is found in young adults but not in children or in older adults. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) cohort, 75% of cases were women. Women were also significantly younger than men (mean 34 years versus 42 years) and had a better prognosis. A gender-specific risk factor, such as oral contraceptives, pregnancy, the puerperium, and hormone replacement therapy, was identified in 65% of women.

**Etiology**

Cerebral venous sinus thrombosis is a serious but potentially treatable disease that predominantly affects young adults, unlike arterial stroke, which is much more commonly with advancing age. Traditionally, CVST is divided into two groups: septic and aseptic. Currently there are more aseptic cases. This disease has been described as a continuing process in which the balance of prothrombotic and thrombolytic process is disturbed, leading to progressive extension of venous thrombosis over time. Several disorders can cause, or predispose patients to, CVST. There are currently more than 100 putative causes and risk factors associated with venous sinus thrombosis. Frequently, more than one cause will be found in an individual patient. The etiology is not identified in ~15 to 35% of cases even after extensive diagnostic investigations. In children, a risk factor was identified in 98% of all cases. Table 13.1 summarizes the most frequent causes.

**Pathology**

Much like deep venous thrombosis, the cerebral venous thrombus begins as a fibrin-rich red thrombus that progressively transforms into fibrous tissue if recanalization does not occur. Thrombosis of the venous structures causes an increase in venous pressure through a delay in venous emptying, decreased capillary perfusion pressure, and increased cerebral blood volume. The effect of the thrombosis on cerebral tissue depends on the availability of collateral venous channels and on the propagation of the thrombus. If there is sufficient venous drainage from collaterals, then only symptoms of headache or those related to intracranial hypertension appear. If venous drainage is insufficient, then the increase in venous and capillary pressure leads to blood–brain barrier disruption, resulting in vasogenic edema as leakage of blood plasma into the interstitial space. A CVST patient can present with no cerebral lesion on imaging or can show evidence of vasogenic edema. Pallor and edema of the cortex and of the adjacent white matter characterize cerebral infarcts macroscopically in the territory drained by a thrombosed vein. In addition, there are multiple petechial hemorrhages that may become confluent, especially in the white matter. These venous infarcts differ significantly from arterial infarcts in having more edema and less necrosis, explaining a much higher potential for recovery. Recently in an animal model of CVST, after inserting a solid graft into the superior sagittal sinus one study showed that apoptosis plays a crucial role during the development of CVST. In the more malignant scenario, unilateral or bilateral hemorrhagic lesions called hemorrhagic venous infarcts occur.
Diagnosis is still frequently overlooked or delayed because of the wide spectrum of clinical symptoms, and subacute presentation or headache-only onset. Most patients present with symptoms that evolved over days or weeks. This variability of clinical features depends on several factors, such as the site and extent of the thrombosis, the rate of propagation of the occlusion, the age of the patient, and the nature of the underlying disease.

Headache is the most common symptom of CVST and occurs in almost 90% of all cases. It is also the most common inaugural symptom, present in 70 to 75% of patients before the onset of other neurologic manifestations.
CVST has no specific features. Its duration is usually a few days, but it may arise suddenly and be severe, mimicking subarachnoid hemorrhage or thunderclap headache. The possibility of isolated headache as the only symptom of CVST has recently been emphasized. The diagnosis of CVST is particularly difficult in such patients, particularly if the results from computed tomography (CT) and cerebrospinal fluid (CSF) testing are normal.\(^2,5,6\) The frequency of various signs and symptoms of CVST are summarized in Table \(\text{13.2}\).

Focal or generalized seizures are more frequently seen in CVST (35–50\%) than in arterial stroke. A very high incidence of seizures (76\%) is seen in peripartum CVST.\(^8\)

Focal neurologic signs are the most common finding in CVST (40–60\% of all cases). Focal deficits in combination with headache, seizures, or an altered consciousness should raise suspicion for CVST as the diagnosis.\(^6\)

Stupor or coma is found in 15 to 19\% of patients at hospital admission and is usually seen in cases with extensive multi-sinus thrombosis or deep venous system involvement causing bilateral thalamic edema. Of all clinical signs reported in CVST, coma at admission is the strongest predictor of poor outcome.\(^3,6\)

According to Bousser and Ferro,\(^2\) four main patterns have been identified:

1. **Isolated intracranial hypertension**: This pattern is associated with headache, nausea, vomiting, papilledema, transient visual obscurations, and eventually sixth nerve palsies. This is the most homogeneous pattern of clinical presentation, accounting for 20 to 40\% of CVST cases.
2. **Focal deficits or partial seizures**: This “focal” pattern, if accompanied by headaches or altered consciousness, should immediately arouse suspicion for CVST.
3. **Subacute diffuse encephalopathy**: This pattern is characterized by a decreased level of consciousness and sometimes seizures without clearly localizing signs. Such cases can mimic encephalitis or metabolic disorders.

<table>
<thead>
<tr>
<th>Presentation</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>80–98</td>
</tr>
<tr>
<td>Papilledema</td>
<td>27–80</td>
</tr>
<tr>
<td>Seizures</td>
<td>10–61</td>
</tr>
<tr>
<td>Motor or sensory deficits</td>
<td>34–37</td>
</tr>
<tr>
<td>Mental status change</td>
<td>10–64</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>12</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td>12</td>
</tr>
<tr>
<td>Cerebellar incoordination</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral or alternating cortical signs</td>
<td>3</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>2</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>2</td>
</tr>
</tbody>
</table>

*Note: Patients may have multiple presentations*

*Source: Adapted from Guenther and Arauz\(^7\) and Poon et al.\(^11\)*
4. **Painful ophthalmoplegia:** This pattern is caused by lesions of the third, fourth, or sixth cranial nerves with additional features of chemosis and proptosis, suggesting cavernous sinus thrombosis. Often because of the masking effect of an inadequate antibiotic regimen, cavernous sinus thrombosis can take a more indolent form with an isolated sixth nerve palsy, mild chemosis, and proptosis.²–⁵

Many other unusual presentations have been described: transient ischemic attacks, attacks of migraine with aura, isolated psychiatric disturbances, tinnitus, isolated or multiple cranial nerve involvement, and subarachnoid hemorrhage.²

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**Neuroimaging**

Given the diverse clinical presentations, appropriate neuroimaging investigations should be performed whenever CVST is suspected.¹ The key to the diagnosis is the imaging of the venous system itself, which may show the occluded vessel or the intravascular thrombus.² Unenhanced CT remains the technique of choice for screening patients with nonspecific clinical presentation and a low suspicion of CVST. Contrast-enhanced CT provides a more accurate diagnosis of CVST. MRI and magnetic resonance (MR) venography have been the noninvasive imaging technique of choice and are often used as the initial diagnostic test for suspicious cases. CT venography is now emerging as a convenient tool for emergency diagnosis, given its widespread accessibility at all hours.¹¹

There are direct and indirect neuroradiological signs to diagnose CVST. Direct signs are seen in only one third of cases¹¹,¹² and are characterized by visualizing the thrombus in the affected vein or sinus. The classic CT findings of CVST are the empty triangle or the empty delta sign, the cord sign, and the dense triangle sign. The empty delta sign is the absence of filling of the torcular on a CT scan after contrast injection (Fig. 13.1a). This sign is absent if the posterior part of the superior sagittal sinus (SSS) is not involved or if the scan has been performed within 5 days of the onset of symptoms. The dense triangle sign or dense clot sign is the demonstration of fresh thrombus in the posterior part of the SSS in a CT scan without contrast administration, whereas the cord sign depicts hyperdense, thrombosed cortical cerebral veins¹³ (Fig. 13.1b). More often, an unenhanced CT shows only the indirect signs of CVST that are caused by brain parenchyma damage as a consequence of the venous outflow obstruction. These are often nonspecific and

---

**Fig. 13.1a–c** Computed tomography (CT) and magnetic resonance imaging (MRI) findings in CVST. (a) Empty delta sign. (b) Cord sign. (c) Venous infarct. (a,b: Courtesy of Dr. Tim W. Watson, University of Calgary, Calgary, Alberta, Canada.)
may include diffuse brain edema, leading to hypoattenuation of the brain (seen in 20–50% of cases). Venous infarction is the most specific indirect sign on unenhanced CT images. An infarct not conforming to a major arterial vascular territory, involvement of a subcortical region with sparing of the cortex, and the presence of multiple isolated lesions are all highly suspicious for CSVT. The infarction may be hemorrhagic or nonhemorrhagic (Fig. 13.1c), and the location of the infarction may give a clue as to the venous structure thrombosed based on the venous drainage involved.11

The gold standard of CVST diagnosis remains digital subtraction angiography (DSA), yet in few cases is it necessary to perform it. CVST diagnosis is most commonly confirmed with MRI and MR venography. MRI is very sensitive for detecting changes in brain parenchyma, formation of blood clots, petechial hemorrhages, and blood flow.7 T1- and T2-weighted spin echo images are able to detect the thrombus. MR venography identifies a filling defect. The T2* echoplanar susceptibility-weighted images may be more helpful in the acute phase when the T1 signal is hypointense and is the most sensitive modality available to detect cortical vein thrombosis. Fluid-attenuated inversion recovery (FLAIR) is able to identify isolated venous occlusion when the sensitivity of T1 and T2 signals is very low. Diffusion weighted imaging (DWI) shows inconsistent patterns of edema, hemorrhage, and infarction within brain parenchyma. Most commonly, the apparent diffusion coefficient is suggestive of vasogenic edema. Taken together, multimodal MRI consisting of T1-, T2-, and T2*-weighted and FLAIR and DWI will detect most cases of CVST (see Case Example 1, below).12

**Laboratory Tests**

The presence of spontaneous CVST during pregnancy or in the puerperium makes the investigation of prothrombotic states necessary to determine the treatment to follow. However, there is no simple confirmatory laboratory test that can confidently rule out CVST in the acute phase of the disease. Several studies have tested the value of D-dimer levels as a diagnostic marker. Low D-dimer levels (< 500 ng/mL) in deep venous thrombosis of the legs have a high negative predictive value. In recent CVST, D-dimer concentrations are usually increased, so a negative D-dimer assay may make the diagnosis of CVST very unlikely. A negative D-dimer assay cannot rule out CVST in the setting of a recent isolated headache.2

Lumbar puncture remains useful in septic patients to rule out bacterial meningitis and to measure and decrease CSF pressure if it is elevated and threatening vision. An abnormal CSF profile is usually seen with an elevated protein level (50%), excessive red blood cells (60%), or leukocytosis (30%).6,8

**Prognosis**

A meta-analysis of several recent prospective series found a 15% rate of death or dependence. In the acute phase, the mortality rate is around 4%.2 A recent study including 3488 patients found an overall mortality rate of 4.4%.14 Of patients with CVST, 75% have complete functional recovery. Several factors are associated with a poor prognosis, such as extremes of age (infancy and advanced age), rapid onset with coma and focal deficits, and thrombosis affecting mainly the deep venous system (see Case Example 2, below). Sepsis and malignancy adversely affects out-
come. \(^3,14\) Twelve percent of patients suffer a recurrence of CVST and 14% a different body location of venous thrombosis. \(^3\)

## Treatment

### Antibiotics

Patients with CVST and a suspected bacterial infection should receive appropriate antibiotics and surgical drainage of purulent collections of infectious sources associated with CVST when appropriate (class I; level of evidence [LOE] C). \(^15\)

### Heparin Therapy

Dose-adjusted intravenous heparin may prevent new venous infarcts, neurologic deterioration, and pulmonary embolism. \(^16\) Based on the limited evidence available, anticoagulant treatment of CVST appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency that did not reach statistical significance. \(^16\) Patients should be treated either with body weight–adjusted subcutaneous low molecular weight heparin (LMWH) or with dose-adjusted intravenous heparin to produce at least a doubling of the activated partial thromboplastin time (aPTT) time (class IIa; LOE B). Concomitant intracerebral hemorrhage (ICH) related to CVST is not a contraindication for heparin therapy. LMWH is preferred in uncomplicated CVST cases, followed by vitamin K antagonists. \(^6,15\)

### Thrombolysis

Endovascular thrombolysis dissolves the thrombus by infusion of a thrombolytic drug into the occluded sinuses. It is often combined with mechanical techniques, such as thrombus disruption, thrombosuction with a rheolytic catheter, and thrombus removal with a balloon catheter. \(^17\) However, currently there is insufficient evidence to support the use of either systemic or local thrombolysis in patients with CVST. \(^17,18\) If patients deteriorate despite adequate anticoagulation and other causes of deterioration have been ruled out, endovascular treatment may be a therapeutic option. Endovascular treatment is not recommended in the setting of ICH or impending herniation from large hemorrhagic infarcts (class IIb; LOE C). The optimal substance, dosage, route (systemic or local), and method of administration (repeated bolus or bolus plus infusion) are not known. \(^6,15\)

### Oral Anticoagulation

Unless there are evident contraindications, oral anticoagulation (OAT) with vitamin K antagonists is generally indicated in all CVST patients after the acute phase. \(^19\) There are insufficient data regarding the optimal duration of OAT in patients with CVST. OAT may be given for 3 months if CVST was secondary to a transient risk factor, such as an infection or trauma. OAT is recommended for 6 to 12 months in patients with idiopathic CVST and in those with “mild” thrombophilia. Indefinite OAT should be considered in patients with two or more episodes of CVST and in those with one episode of CVST and “severe” thrombophilia (class IIb; LOE C). \(^6,15\)
Target ranges for the international normalized ratio are the same as in deep venous thrombosis of the leg (i.e., 2.0–3.0).\textsuperscript{19}

### Antiepileptic Drugs

In the absence of seizures, the routine use of antiepileptic drugs in patients with CVST is not recommended (class III; LOE C). In patients with a single seizure due to a parenchymal lesion, early initiation of antiepileptic drugs is recommended to prevent further seizures. The optimal duration of treatment for patients with seizures is unclear;\textsuperscript{6,15} some authors suggest continuing antiepileptic drugs for 1 year before tapering for patients with early seizures and hemorrhagic lesions on admission brain scan, whereas in patients without these risk factors antiepileptic therapy may be tapered off gradually soon after the acute stage.\textsuperscript{8,19}

### Treatment of Elevated Intracranial Pressure

There are no controlled data about the risks and benefits of certain therapeutic measures to reduce an elevated intracranial pressure in patients with CVST. However, based on the available evidence, steroids should be avoided (class III; LOE B). Acetazolamide is a reasonable option in cases of intracranial hypertension to alleviate symptoms. Other therapies (lumbar puncture, optic nerve decompression, or shunts) can be effective if there is progressive visual loss (class IIa, LOE C). In patients with neurologic deterioration due to severe mass effect or intracranial hemorrhage causing intractable intracranial hypertension, decompressive hemicraniectomy may be considered (class IIb; LOE C).\textsuperscript{6,15} Prompt decompressive surgery (decompressive craniectomy, hematoma evacuation, or both) can be lifesaving and result in good neurologic outcome in CVST patients with impending transtentorial herniation. Additional prospective data on the efficacy of decompressive surgery are needed.\textsuperscript{19–21}

### Case Example 1

A 25-year-old woman on oral contraceptive pills (OCPs) for 5 years presented at the hospital with 5 days of progressively worsening severe headache with nausea, vomiting, and diplopia. She had a known history of classic migraine with visual auras since 15 years of age. Physical exam showed bilateral sixth nerve palsies, drowsiness, and loss of venous pulsations in both fundi; pupils were equal, she was hyperreflexic throughout, and afebrile (Figs. 13.2 and 13.3). After treatment, the patient had a full neurological recovery.

### Case Example 2

A 36-year-old woman, previously healthy, on OCPs presented to the emergency department with a confusional status preceded by 5 days of headache and nausea without vomiting. Fig. 13.4 illustrates the CVST findings on CT and multimodal MRI. The thrombophilia workup was negative. The patient had a full neurologic recovery, but after the CVST presented for several years, anxiety, depression, and tension-type headache were noted.
Fig. 13.2a–f Case example 1. Initial CT scan showing a thrombus in the left transverse (a,b), straight (c), and extension to the sagittal sinuses (d–f). (Courtesy of Dr. Tim W. Watson, University of Calgary, Calgary, Alberta, Canada.)

Fig. 13.3 Case example 1, continued. (a) Magnetic resonance venography with a thrombus seen in the sagittal sinus. (b,c) Axial MRI showing a thrombus in the right transverse (b) and straight sinus (c). (Courtesy of Dr. Tim W. Watson, University of Calgary, Calgary, Alberta, Canada.)
KEY POINTS

- Cerebral venous sinus thrombosis is an uncommon condition (1% of all strokes) characterized by extreme variability in its age of onset and clinical presentation.
- Symptoms include headache, seizures, neurologic deficits, and altered consciousness.
- The mode of onset is highly variable, from sudden to progressive over weeks, so that CVST can mimic a host of conditions.
- A high index of clinical suspicion is needed to diagnose this uncommon condition so that appropriate treatment can be initiated.
- The present gold standard for the diagnosis of CVST is no longer cerebral angiography but rather multimodal MRI with MR venography or CT venography.
- Heparin is the first-line treatment for CVST because of its efficacy and safety.
- Venous infarcts are frequently overlooked because CVST is an uncommon cause of stroke. Venous infarctions typically cross arterial territories and spare cortex due to vasogenic edema. The degree and extent of hypopattenuation is out of keeping with the extent of neurologic deficits. An arterial infarct of similar size results in much more severe neurologic deficits.
- Cerebral venous sinus thrombosis has a benign course if it is diagnosed and treated early. Complete functional recovery occurs in most cases (75%). The mortality rate is low (~5%).
- Anticoagulation shifts the balance in favor of thrombus dissolution rather than propagation.
- More aggressive treatments such as decompressive hemicraniectomy or endovascular treatment with local thrombolysis or transvenous thrombectomy may be required in more fulminant cases.

Fig.13.4a–d  Case example 2. Computed tomography scan and MRI reveals internal cerebral vein thrombosis. (a) Note the bilateral thalamic edema with petechial hemorrhage in the right thalamus. (b) T1-weighted MRI sequence showing internal cerebral vein thrombosis with extension of clot into the vein of Galen and straight sinus (hyperintensities). (c) Fluid-attenuated inversion recovery (FLAIR) MRI sequence showing the bilateral thalamic edema. (d) Sagittal T1-weighted MRI sequence revealing internal cerebral vein thrombosis with extension of clot into the vein of Galen and straight sinus (hyperintensities). (Case example and illustrations courtesy of Dr. Carlos Cantu-Brito, National Institute of Medical Sciences and Nutrition Salvador Zubirán [INCMNSZ], Mexico City, Mexico.)
Deep venous thrombosis has a malignant course resulting in decreased level of consciousness (LOC) if diagnosis and treatment are not initiated quickly. Bilateral thalamic hypoattenuation is typical of deep venous thrombosis and may still represent reversible vasogenic edema. Aggressive treatment intervention may result in a good clinical outcome.

**REVIEW QUESTIONS**

1. The mainstay treatment of cerebral thrombosis is:
   A. Anticoagulation with Heparin
   B. Acetylsalicylic acid (ASA)
   C. Endovascular treatment
   D. Hypertonic saline

2. The most consistent predictor of a poor outcome with cerebral venous thrombosis is:
   A. Coma at presentation
   B. Focal neurologic deficit
   C. Ophthalmoplegia
   D. Seizures

3. The current most convenient method for ascertaining the diagnosis of CVST currently is:
   A. Cranial ultrasound
   B. CT venogram
   C. Diagnostic catheter angiogram
   D. Serum D-dimer

4. The most appropriate initial therapy following the diagnosis of cerebral venous sinus thrombosis is:
   A. ASA
   B. Endovascular thrombolysis
   C. Intravenous heparin
   D. Oral anticoagulation (warfarin)

5. A 40-year-old woman presents with headache and raised intracranial pressure. MR venography demonstrates a transverse and sigmoid sinus thrombosis on the right side. Two years ago, she had an unprovoked pulmonary embolus that was treated with oral anticoagulation for 6 months. The most appropriate therapy for this condition is:
   A. Intravenous heparin followed by lifelong oral anticoagulation
   B. Intravenous heparin followed by oral anticoagulation for 3 months
   C. Intravenous heparin followed by ASA therapy
   D. Low molecular weight heparin for a period of 3 months

6. Which of the following is not a recommended option for managing elevated intracranial pressure in patients with cerebral venous sinus thrombosis?
   A. Acetazolamide
   B. External ventricular drain
   C. Lumbar drain
   D. Optic nerve sheath fenestration
   E. Steroids
References

<table>
<thead>
<tr>
<th>ANSWER KEY</th>
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<tbody>
<tr>
<td>1. A</td>
</tr>
<tr>
<td>2. A</td>
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<tr>
<td>3. B</td>
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<tr>
<td>4. C</td>
</tr>
<tr>
<td>5. A</td>
</tr>
<tr>
<td>6. E</td>
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Management of Bleeding and Coagulation in the Neurosurgical Perioperative Period
Specific Anticoagulant and Antiplatelet Agent Reversal Strategies for Neurosurgical Patients
Shahid M. Nimjee and Gerald A. Grant

In 1916, a medical student named Jay McLean stumbled across a substance that inhibited blood coagulation.\(^1\) It was not until approximately 20 years later that heparin was isolated in enough quantity to use clinically.\(^2\) Since that time, numerous anticoagulant and antiplatelet agents have been developed to treat pathological thrombosis.

Pathological processes requiring anticoagulation and antiplatelet therapy in neurology may include venous sinus thrombosis, ischemic stroke, intracranial stent-assisted coiling, and carotid and vertebral artery dissection. However, many patients brought to the attention of neurosurgeons are prescribed anticoagulant and antiplatelet drugs to treat coronary and peripheral vascular disease, or are prescribed anticoagulants as protection from venous thromboembolism after orthopedic surgery. The challenges faced by neurosurgeons may include how to effectively reverse these agents in a timely manner, deciding what method is most appropriate, and determining whether to observe the patient or emergently take the patient to the operating room.

This chapter briefly reviews the anticoagulants and antiplatelet agents that are currently used, identifies the reversal agents of each of these drugs, and discusses their mechanism of action, dose, and indications (Tables 14.1 and 14.2).

Anticoagulant Agents

Heparins

Unfractionated heparin is the most commonly used inpatient anticoagulant in patients with neurologic disorders. It is a polyglycosaminoglycan that binds to exosite 2 on thrombin (factor IIa [FIIa]) as well as coagulation factor Xa (FXa).\(^3\) The preference for binding to FIIa over FXa is largely due to its molecular weight, which ranges from 15 to 30 kd. The activity of heparin is measured using an activated partial thromboplastin time (aPTT). It has a relatively short half-life (\(t_{1/2}\)) of 1 to 2 hours; therefore, after discontinuation of heparin, coagulation returns to baseline in approximately 3 to 4 hours. Heparin can be reversed using protamine, a positively charged molecule that binds to negatively charged heparin, preventing it from binding to thrombin. The effective dose of protamine is 1 mg per 100 IU of heparin. Protamine should be dosed based on the amount of active heparin in circulation, so if 1000 IU of heparin has been administered over 2 hours, patients should receive 20 mg of protamine in order to fully reverse the activity of heparin.

Low molecular weight heparin (LMWH) is fractionated form of heparin with a molecular weight of 8 to 15 kd.\(^3\) The shorter length results in preference for FXa
<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Mechanism</th>
<th>Antidote</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Largely anti-IIa with mild anti-Xa</td>
<td>Protamine sulfate</td>
<td>1 mg of protamine per 10 IU of heparin</td>
</tr>
<tr>
<td>Low molecular weight heparin (LMWH)</td>
<td>Largely anti-Xa with mild anti-IIa</td>
<td>Protamine sulfate</td>
<td>1 mg of protamine per 100 IU of LMWH</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Inhibit FXa</td>
<td>Recombinant FVII complex concentrate</td>
<td>80 μg/kg Transfuse, follow modified PT (calibrated for rivaroxaban) or anti-Xa assay</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Inhibit FXa</td>
<td>Recombinant FVII complex concentrate</td>
<td>80 μg/kg Transfuse, follow modified PT (calibrated for rivaroxaban) or anti-Xa assay</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Univalent inhibition of FIIa site</td>
<td>None</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Univalent inhibition of FIIa site</td>
<td>None</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Bivalent inhibition of FIIa active site</td>
<td>None</td>
<td>Stop intravenous administration of drug</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Bivalent inhibition of FIIa active site</td>
<td>None</td>
<td>Stop intravenous administration of drug</td>
</tr>
<tr>
<td>Desirudin</td>
<td>Bivalent inhibition of FIIa active site</td>
<td>None</td>
<td>Stop intravenous administration of drug</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Inhibits vitamin K-dependent clothing factors II, VII, IX, and X</td>
<td>Vitamin K</td>
<td>1–2 mg SC every 12 hours Transfuse, follow INR</td>
</tr>
<tr>
<td>Aacenocoumarol</td>
<td>Inhibits vitamin K-dependent clothing factors II, VII, IX, and X</td>
<td>Vitamin K</td>
<td>1–2 mg SC every 12 hours Transfuse, follow INR</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>Inhibits vitamin K-dependent clothing factors II, VII, IX, and X</td>
<td>Vitamin K</td>
<td>1–2 mg SC every 12 hours Transfuse, follow INR</td>
</tr>
<tr>
<td>Anisindione</td>
<td>Inhibits vitamin K-dependent clothing factors II, VII, IX, and X</td>
<td>Vitamin K</td>
<td>1–2 mg SC every 12 hours Transfuse, follow INR</td>
</tr>
<tr>
<td>Abbreviations: COX, cyclooxygenase; DAVP, deamino-D-arginine vasopressin; FFP, fresh frozen plasma; LMWH, low molecular weight heparin; PCC, prothrombin complex concentrate; PFA, platelet function analyzer; TXA₂, thromboxane A₂.</td>
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<table>
<thead>
<tr>
<th>Antiplatelet Agent</th>
<th>Mechanism</th>
<th>Antidote</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Inhibits platelet COX-1, preventing TXA₂, important in platelet activation</td>
<td>Platelets</td>
<td>1 U to start, follow PFA 0.3 μg/kg</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Inhibits P2Y₁₂, an ADP receptor required for platelet activation</td>
<td>Platelets</td>
<td>1 U to start, follow PFA 0.3 μg/kg</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Inhibits P2Y₁₂, an ADP receptor required for platelet activation</td>
<td>Platelets</td>
<td>1 U to start, follow PFA 0.3 μg/kg</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Inhibits GPIIb/IIIa, final pathway for platelet activation</td>
<td>Platelets</td>
<td>1 U to start, if volume is an issue, use concentrated platelets and PCC over FFP</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Inhibits GPIIb/IIIa, final pathway for platelet activation</td>
<td>Platelets</td>
<td>1 U to start, if volume is an issue, use concentrated platelets and PCC over FFP</td>
</tr>
<tr>
<td>Abbreviations: COX, cyclooxygenase; DAVP, deamino-D-arginine vasopressin; FFP, fresh frozen plasma; LMWH, low molecular weight heparin; PCC, prothrombin complex concentrate; PFA, platelet function analyzer; TXA₂, thromboxane A₂.</td>
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</table>
Anticoagulant and Antiplatelet Agent Reversal Strategies

The half-life of LMWH is approximately 4 hours, so it usually takes several hours to return to a normal coagulation profile after drug administration. Protamine is also used to reverse the activity of LMWH, but it is only effective in reversing approximately 50% of the anti-Xa activity. Protamine is administered at a dose of 1 mg for every 1 mg dose of LMWH administered over the previous 6 to 8 hours.

Factor Xa Inhibitors

There are two classes of FXa inhibitors: pentasaccharides and an oral direct inhibitor of FXa. The two available pentasaccharides are fondaparinux and idraparinux, which has been discontinued. Fondaparinux has a shorter half-life of 17 hours compared with idraparinux, which is almost 80 hours. The only effective means of reversing the activity of these compounds is administering recombinant factor VIIa (rFVIIa), with an initial dose of 80 μg/kg.

Rivaroxaban is an orally available direct FXa inhibitor with a half-life of 7 to 11 hours. It does not require monitoring, but it will increase the prothrombin time (PT). Reversal of this compound can be achieved using prothrombin complex concentrate, administering it intravenously and following either a PT or an anti-FXa assay.

Direct Thrombin Inhibitors

These compounds bind to the active site of thrombin and include both intravenous and oral forms and univalent and divalent classes. Argatroban is an intravenous, univalent formulation with a half-life of 50 minutes. Dabigatran is an orally available drug with a half-life of 12 to 17 hours. Bivalirudin, lepirudin, and desirudin are bivalent intravenous drugs that have half-lives of between 25 and 75 minutes. Unfortunately, this is the only class of anticoagulants that cannot be reversed by available agents, including rFVIIa and prothrombin complex concentrate (PCC). The bivalent, intravenous direct thrombin inhibitors should immediately be discontinued to return to baseline coagulation function, which can be verified by determining the thrombin time. Hemodialysis has been used to help with the reversal of dabigatran.

Vitamin K–Dependent Clotting Factor Inhibitors

The discovery of this class of anticoagulant dates back to the 1920s, when scientists observed that cattle that ingested a particular type of clover would die of a hemorrhagic illness. Subsequent work led to isolating a compound, called coumarin, that prevents blood clotting. Today, warfarin is the most commonly prescribed oral anticoagulant, although it is associated with an increased risk of intracerebral hemorrhage (ICH) and ICH-related mortality. It inhibits vitamin K–dependent clotting factors in the liver, including factors II, VII, IX, and X, as well as protein C and S. Warfarin belongs to a class of compounds called coumarins that contain 4-hydroxycoumarin, which inhibits vitamin K epoxide reductase, leading to inhibition of the above-mentioned clotting factors. Other drugs in this class include acenocoumarol, phenprocoumon, and anisindione. The half-lives of these com-
pounds range from 18 hours to 10 days. Coumarin levels are followed by testing the prothrombin-time international normalized ratio (PT-INR or INR).

The reversal strategy for coumarins depends on the urgency of reversal. Elective reversal entails using intravenous vitamin K at a dose of 1 to 2 mg administered by subcutaneous injection every 12 hours. There is no proven advantage to intravenous administration unless the patient is experiencing hemodynamic problems (shock). The reversal effect begins within 2 hours of the first injection, and reversal is usually achieved in 12 to 16 hours. Oral administration of vitamin K can take over 24 hours to reverse the activity of coumarin.

For urgent reversal, fresh frozen plasma (FFP) or PCC is appropriate. The concentration of clotting factors in PCC is 60-fold higher than that in FFP, and PCC also has a more sustainable reversal phenotype. PCCs include inactivated plasma-derived concentrates of factor IX, with varying amounts of factors II, VII, and X, and protein C and S, and they work rapidly to reverse anticoagulation by replacing the vitamin K–dependent factors. The use of FFP depends on the time required to obtain the ABO blood type. PCCs are reconstituted quickly and can be given via an intravenous bolus over 2 to 5 minutes. A drawback of PCC is that it can lead to a hypercoagulable state, placing the patient at risk of arterial or venous thrombosis. Although vitamin K and FFP are routinely used to reverse anticoagulation, neither provides rapid INR reversal. Therefore, other options have been explored, including PCC, described above, and rFVIIa.

If an emergency reversal in the operating room is needed, rFVIIa can be administered. It is a vitamin K–dependent glycoprotein that produces hemostasis by activating the extrinsic pathway. Recombinant FVIIa has a rapid onset of action and a short half-life of 2 to 3 hours. It is administered at an initial dose of 80 µg/kg, based on research evaluating doses to limit the size of the blood clot in patients with acute intracranial hemorrhage. It is still important to follow-up with administering FFP or PCC as well as vitamin K after the rFVIIa has been given. Although the INR reduces quickly, it will probably not be sustained, given the short duration of action, and rFVIIa does not replace other vitamin K–dependent clotting factors inhibited by warfarin. It is not as clear, however, how frequently to repeat the rFVIIa doses. A concern associated with rFVIIa is its potential to lead to acute thromboembolism. Mayer et al found that 80 µg/kg of rFVIIa was associated with a 5% absolute increase in the frequency of serious arterial thromboembolic events, despite the exclusion of patients thought to be at high risk.

**Antiplatelet Agents**

**Nonsteroidal Anti-Inflammatory Drugs**

Aspirin is a salicylate that was synthesized in 1899 by Bayer originally to treat rheumatism. Its antiplatelet activity results from irreversibly binding to cyclooxygenase-1 (COX-1), thereby inhibiting thromboxane A2 (TXA2), which is an important catalyst in platelet activation. It works within minutes of ingestion, and although it has a relatively short half-life of 3 hours, its pharmacokinetic profile renders it effective for the life of the platelet (7–10 days).

The standard of measurement in platelet inhibition is a platelet function analyzer, PFA-100. This is an ex-vivo whole blood assay that aspirates blood through an aperture on a collagen surface and measures the closing time. The normal clos-
ing time is between 60 and 120 seconds, depending on whether a collagen epi-
ephrine cartridge or collagen adenosine phosphate (ADP) is used.\textsuperscript{24}

When possible, it is best to avoid the use of aspirin for 7 to 10 days before
elective surgery unless the clinical condition requires continued administration
(e.g., carotid endarterectomy). To reverse the activity of aspirin, two strategies are
employed. The first is administration of platelets with the goal of replacing aspirin-
bound platelets with free circulating cells. Recently, a study found that administer-
ing platelets to patients with traumatic brain injury who are taking aspirin showed
a dose-response relationship in reversing platelet inhibition.\textsuperscript{25} The second method
is administration of deamino-D-arginine vasopressin (DDAVP), which enhances
platelet adhesion by releasing FVIII and von Willebrand factor (vWF), which are
essential factors in platelet adhesion.\textsuperscript{26} The dose of DDAVP is 0.3 $\mu$g/kg in saline
administered over 30 minutes.

**Thienopyridines**

Clopidogrel and prasugrel are thienopyridine molecules that inhibit platelet func-
tion by binding to the ADP receptor P2Y\textsubscript{12}. The PFA-100 can be used to evaluate
platelet inhibition using collagen ADP cartridges.\textsuperscript{24}

The strategy for reversal is similar to that for aspirin, using both platelet and
DDAVP at a dose 0.3 $\mu$g/kg.\textsuperscript{27,28}

**Glycoprotein IIb/IIIa Inhibitors**

Glycoprotein IIb/IIIa (GPIIb/IIIa) is an integrin found on the surface of platelets and,
once activated, it converts from a quiescent to activated structure and binds fibrin-
ogen, resulting in platelet aggregation.\textsuperscript{29,30} Abciximab, a chimeric human-murine monoclonal antibody was the first
GPIIb/IIIa antagonist developed. Eptifibatide, a small peptide, interacts with and
inhibit the function of the $\beta_3$-subunit of GPIIb/IIIa. This subunit specifically recog-
nizes an arginine-glycine-aspartic acid (AGD) residue on proteins such as vWF and
fibrinogen and binds to it to form a platelet aggregate.\textsuperscript{31} Abciximab has a relatively
short half-life but has high affinity for GPIIb/IIIa, resulting in platelet inhibition
that can take 4 to 5 days to return to normal. Eptifibatide has a relatively low affin-
ity for its target, such that the antiplatelet effect usually diminishes within hours
after discontinuing the intravenous infusion, provided that the patient has normal
renal function.

Reversal strategies for GPIIb/IIIa inhibitors involve stopping administration of
the drug and administration of platelet concentrate and fibrinogen by FFP or PPC.\textsuperscript{32}
A PFA-100 can be used to follow platelet inhibition and reversal.

**Conclusion**

Pathological thrombosis results in cardiovascular, cerebrovascular, and peripheral
vascular disease, and represents the most common cause of morbidity and mortal-
ity in the Western world. Anticoagulant and antiplatelet therapy have improved
the outcome in these patient populations.\textsuperscript{33} These drugs, however, do not come
without significant risk, chief among them being hemorrhage.\textsuperscript{34} When patients
present with hemorrhage or with the need for other emergent or urgent neuro-
surgical treatment, be it in the brain or spine, urgent anticoagulant or antiplate-
let reversal is usually required.

The reversal for both anticoagulant and antiplatelet drugs also carries risks,
including venous thromboembolism, stroke, and myocardial infarction. This is fur-
ther complicated in the setting of combined aspirin-Plavix therapy in patients who
have intracranial or cardiac stents. Neurosurgeons must weigh the risk of reversal
with the potential morbidity and mortality of not treating the patient with an
intracerebral or intraspinal hemorrhage.

KEY POINTS

• Patient history, PT, PTT, and platelet count are clinically valuable when
screening adult neurosurgery patients for the risk of postoperative bleeding.
• Platelet count determination is clinically valuable for adult patients to rule
out thrombocytopenia.
• Prothrombin time (PT) assesses the extrinsic and common pathways of
clotting and is typically expressed in the international normalized ratio
(INR) format.
• Activated partial thromboplastin time (aPTT) tests the integrity of the in-
trinsic and common pathways of coagulation.
• Routine PT and PTT assessment are typically recommended to screen for
problems of hemostasis in neurosurgery patients undergoing surgery, but
the value of routine screening has not been validated in any randomized
trials. Although recommended, they may at most provide baseline values.
• A disseminated intravascular coagulation (DIC) panel is not typically used
but may be required if there are indicators that suggest uncontrolled co-
agulation or bleeding. The DIC panel includes D-dimer (which increases),
fibrinogen level (which decreases), and fibrinogen degradation products
(FDPs, which increase). Platelet count also decreases.
• Coagulation screening tests can be meaningfully interpreted only with the
knowledge of their limitations and the relevant clinical situation.

REVIEW QUESTIONS

1. Strategies for reversing the effects of warfarin include:
   A. Vitamin K 10 mg intravenous (IV)
   B. Vitamin K 1–2 mg subcutaneous (SC)
   C. Fresh frozen plasma infusion
   D. Platelet infusion
   E. Prothrombin complex concentrate

2. How many days before most elective surgery should aspirin or clopidogrel
   should be stopped:
   A. 1 to 2
   B. 2 to 3
   C. 3 to 4
   D. 4 to 5
   E. 5 to 10
3. The most effective strategy for reversing the effects of unfractionated heparins is:
   - A. Platelet transfusion
   - B. DDAVP
   - C. Protamine 0.1 mg/100 IU heparin
   - D. Protamine 1 mg/100 IU heparin
   - E. Fresh frozen plasma infusion

4. Which of the following are factor Xa inhibitors?
   - A. Fondaparinux
   - B. Rivaroxiban
   - C. Idraparinux
   - D. Dabigatran
   - E. Bivalirudin

5. Which of the following are direct thrombin inhibitors?
   - A. Fondaparinux
   - B. Rivaroxiban
   - C. Idraparinux
   - D. Dabigatran
   - E. Bivalirudin

6. Effective strategies for rapidly reversing the effects of aspirin include:
   - A. Prothrombin complex concentrate
   - B. Platelet infusion
   - C. Vitamin K 1 to 2 mg SC
   - D. DDAVP IV
   - E. Fresh frozen plasma infusion

References


Intracranial and spine surgeries are associated with a high risk for bleeding complications. Thus, patients receiving chronic oral anticoagulant and antiplatelet therapies present a significant challenge for the neurosurgeon.¹ Many of these patients require bridging therapy and alteration of antiplatelet regimens to minimize the risks of surgical complications. Unfortunately, there is minimal evidence-based literature pertaining to specific guidelines for these patients on appropriate reinitiation of anticoagulant and antiplatelet therapy in the postoperative period. Therefore, extrapolation of recommendations presented for nonneurosurgical patients must be considered. The 2008 American College of Chest Physicians (ACCP) Guidelines are used to provide a framework for decision making.² The most recent 2012 ACCP guidelines,³ although changing the way in which quality of evidence and grades of recommendations were established, did not result in any substantive change from the 2008 recommendations.

Classes of Agents

Antiplatelet therapy is used to decrease platelet aggregation and inhibit thrombus formation in the arterial circulation. The most clinically relevant of these drugs are cyclooxygenase inhibitors (aspirin), adenosine diphosphate (ADP) receptor inhibitors (clopidogrel, prasugrel, and ticlopidine), nonsteroidal anti-inflammatory drugs (NSAIDs), glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban), and adenosine deaminase and phosphodiesterase inhibitors (dipyridamole). Aspirin and clopidogrel are commonly used for primary and secondary prevention of thrombotic cardiovascular and cerebrovascular disease. As these two agents have been widely studied, evidence-based guidelines for reinitiation of therapy are established and will be presented below. As the majority of these other medications are used in the acute setting for treatment of cardiovascular events, perioperative management should be done in conjunction with a cardiologist.

Chronic oral anticoagulation (AC) with warfarin is indicated in four primary classes of disorders: cardiovascular disease, cerebrovascular disease (CVD), venous thromboembolism (VTE), and peripheral vascular disease (PVD). PVD includes arterial stenosis and bypass grafts. Patients with a history of upper- and lower-extremity deep vein thrombosis (DVT) or pulmonary embolism (PE) encompass the VTE group. Those in the CVD group include cardiogenic or atherosclerotic stroke and carotid dissection. Lastly, cardiovascular diseases necessitating anticoagulation include valvular disease with or without prosthetic valves, idiopathic dilated cardiomyopathy, intracardiac thrombus, and atrial fibrillation.¹ Each of these disease subsets represents patients with an increased risk for thromboembolic com-
applications requiring bridging anticoagulation therapy in the periprocedural setting. In fact, the ACCP recommends that those patients with an estimated annual thrombotic risk > 4% in the absence of anticoagulation receive bridging therapy.

Pre- and periprocedural strategies for bridging therapy have previously been defined for these patients, but it is important to note that bridging therapy by definition is inclusive of therapeutic unfractionated heparin (UFH) and low molecular weight heparin (LMWH), as well as low-dose LMWH. Postoperative initiation of UFH or LMWH requires individualized assessment of bleeding and thromboembolic risk in all postoperative patients. The delicate balance between perioperative risk of thromboembolism and bleeding is especially prevalent in neurosurgical cases. Ensuring the safety of these high-acuity patients requires great care and consideration of risk stratification, procedure type, and case-by-case assessment of postoperative bleeding (Table 15.1).

### Postoperative Resumption of Anticoagulant and Antiplatelet Therapy

The 2008/2012 ACCP guidelines\(^2,3\) are considered the authoritative source of recommendations for postoperative resumption of anticoagulant and antiplatelet therapy. These guidelines provide recommendations classified by a grading system incorporating assessment of benefit to risk ratio (class 1 and 2), and methodological strength (A through C). Specifically, grade 1 represents strong recommendations such that benefits of therapeutic choice outweigh risk, and grade 2 represents those that are weak, in which the trade-off is less clear. Methodological strength is assessed such that high-quality evidence from randomized trials (strength A) is distinguished from moderate-quality evidence from randomized trials with limitations (strength B), and from observational studies with large effects and low-quality evidence (strength C).\(^2\)

All guidelines to date regarding the reinitiation of postoperative anticoagulation and antiplatelet therapy are based on grade 1B/C and 2C recommendations. It is well known that there are limited data from randomized controlled studies in this area, as the risk of adverse outcomes in this population far outweighs the possibility of gathering relevant data. This factor highlights the primary importance of evaluating each patient on an individualized case-by-case basis. This evaluation should be based on the degree of postoperative bleeding and level of risk for the development of thromboembolic events.

Every neurosurgical patient is considered at high perioperative bleeding risk, and the degree of postoperative hemostasis will be the primary determining factor to decide when anticoagulant and antiplatelet therapy can be restarted. Patients should not resume anticoagulation until primary hemostasis is secured. Postoperative screening coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT]) should be normal, and the patient’s platelet count should be ≥ 100,000/µL. If postoperative hemostatic abnormalities exist, they should be evaluated and corrected as discussed in Chapter 14.

A secondary consideration prior to restarting anticoagulant and antiplatelet therapy postoperatively is the patient’s risk for thromboembolic complications. This risk is based on preoperative comorbidities (Table 15.2). The degree of intensity used when restarting anticoagulation (therapeutic versus low-dose UFH/LMWH versus no anticoagulation) will be determined by the preoperative condition necessitating chronic oral anticoagulation. No risk stratification model has yet to be
### Table 15.1 Characteristics of Commonly Used Anticoagulant and Antiplatelet Agents

<table>
<thead>
<tr>
<th>Activity</th>
<th>Peak Concentration/Anticoagulant Effect</th>
<th>Half-Life</th>
<th>Therapeutic Dosing</th>
<th>Recommended Time of Discontinuation Prior to Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>2–4 hours</td>
<td>90 minutes</td>
<td>15–18 U/kg ± bolus with titration to goal aPTT</td>
<td>4 hours</td>
</tr>
<tr>
<td>LMWH</td>
<td>3–5 hours</td>
<td>6 hours</td>
<td>1 mg/kg SQ bid</td>
<td>24 hours</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Partial effect at ~ 48 hours with INR ~ 1.5</td>
<td>36–42 hours</td>
<td>2–10 mg daily</td>
<td>5–6 days</td>
</tr>
<tr>
<td>ASA</td>
<td>Minutes to hours</td>
<td>Dose dependent (15 minutes–10 hours)</td>
<td>81–325 mg daily</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>3–7 days</td>
<td>6 hours</td>
<td>75 mg daily ± loading dose</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Minutes to hours (combined with ASA)</td>
<td>10 hours</td>
<td>200 mg dipyridamole ± 25 mg ASA daily</td>
<td>7–10 days</td>
</tr>
</tbody>
</table>

Abbreviations: ADP, adenosine diphosphate; PTT, partial thromboplastin time; GPIIb/IIIa, glycoprotein IIb/IIIa; UFH, unfractionated heparin; LMWH, low molecular weight heparin; ASA, acetylsalicylic acid.
Table 15.2 American College of Chest Physicians (ACCP)-Recommended Risk Stratification for Perioperative Thromboembolism

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mechanical Valve</th>
<th>Atrial Fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• Any mechanical mitral valve</td>
<td>• CHADS₂ of 5 or 6</td>
<td>• Recent VTE (&lt; 3 months)</td>
</tr>
<tr>
<td></td>
<td>• M/A caged ball or tilting disk valve</td>
<td>• Recent stroke or TIA (&lt; 3 months)</td>
<td>• Severe thrombophilia</td>
</tr>
<tr>
<td></td>
<td>• Recent (&lt; 6 months) stroke or TIA</td>
<td>• Rheumatic heart disease</td>
<td>• Deficiency of protein C/S, antithrombin</td>
</tr>
<tr>
<td>Moderate</td>
<td>• Bi-leaflet AVR with major risk factors for stroke</td>
<td>• CHADS₂ of 3 or 4</td>
<td>• VTE within 3–12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Nonsevere thrombophilia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Active cancer</td>
</tr>
<tr>
<td>Low</td>
<td>• Bi-leaflet AVR without major risk factors for stroke</td>
<td>• CHADS₂ 0–2</td>
<td>• VTE ≥ 12 months ago</td>
</tr>
<tr>
<td></td>
<td></td>
<td>without prior stroke or TIA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TIA, transient ischemic attack; AVR, aortic valve replacement; VTE, venous thromboembolism; ATE, arterial thromboembolism; Ab, antibody; M/A, mitral/aortic.

Notes: High risk: > 10%/year risk of ATE or > 10%/month risk of VTE.
Moderate risk: 4–10%/year risk of ATE or 4–10%/month risk of VTE.
Low risk: < 4%/year risk of ATE or < 2%/month risk of VTE.

Source: Table extracted from the 2008 ACCP Guidelines for perioperative management of antithrombotic therapy. The table depicts indications for anticoagulant therapy based on thromboembolic risk (high, moderate, low). Each level of risk has related conditions listed.

validated, but the ACCP separates patients into high-risk, moderate-risk, and low-risk groups depending on the initial indication for antithrombotic therapy. Those patients requiring bridging therapy will incorporate both moderate- and high-risk groups, and thus represent the population for which this discussion is appropriate.

The ACCP guidelines present class 1C recommendations for patients receiving bridging anticoagulation undergoing surgical procedures with high bleeding risk (all neurosurgical cases). These include (1) delay starting LMWH/UFH until 48 to 72 hours after surgery when hemostasis is secured, (2) administer low-dose LMWH/UFH when hemostasis is secured, or (3) completely avoid LMWH or UFH and just restart warfarin. Additional 1C recommendations state that the individual anticipated bleeding risk and degree of postoperative hemostasis should determine the time to restart UFH or LMWH rather than starting anticoagulation at a fixed period of time.

Vinik et al⁴ have proposed an approach to resumption of anticoagulation with UFH/LMWH in patients undergoing bridging therapy (Fig. 15.1). This approach assumes that postoperative hemostasis is normal. It can be extrapolated from their proposal that in neurosurgical patients (high bleeding risk) at least 24 hours post-procedure, those with high or moderate thromboembolic risk should be started on
low-dose UFH/LMWH or no anticoagulation at all.\textsuperscript{1,4} Additionally, on postoperative day 2 or 3, the UFH/LMWH dose used should be reevaluated. Patients receiving no anticoagulation who are not bleeding should be started on low-dose therapy. Patients already on low-dose anticoagulation who are without bleeding should be advanced to therapeutic dosing.

The primary purpose of bridging anticoagulation is to provide a window in which warfarin therapy is discontinued and the risk of thromboembolic events is minimized. As is noted in Table 15.1, at least 2 days of warfarin therapy are necessary to minimally achieve a partial anticoagulant effect (international normalized ratio [INR] ≥ 1.5). For this reason, ACCP guidelines have a 1B recommendation for restarting warfarin on (1) the evening of the day of surgery, (2) on postoperative day 1, or (3) when adequate hemostasis is achieved. Unfortunately, these recommendations are not based on the neurosurgical literature and cannot provide an easy one-size-fits-all solution for neurosurgical patients. Many neurosurgeons may prefer to withhold full anticoagulation until they are comfortable that the patient is at minimal risk for bleeding complications, which typically is on postoperative days 3 to 4 but may be up to 1 week postsurgery.

When warfarin is restarted, the patient can either receive the preoperative warfarin dose or have the home dose doubled for the first 2 days after reinitiation. Numerous studies have indicated that to achieve a therapeutic INR (2.0–3.0), 4 to 7 days of bridging anticoagulation will be necessary, with the choice of regimen differing by approximately a half-day. The guidelines support the idea that once a therapeutic INR is reached, UFH/LMWH can be discontinued. Importantly, daily INR monitoring in all hospitalized patients should be done beginning the morning
after initial dosing until a therapeutic INR is reached, and should be continued twice weekly thereafter.\textsuperscript{5}

Many patients require antiplatelet therapy that cannot be discontinued in the perioperative period (bare metal stents within 6 weeks of placement, or within 12 months of drug-eluting stent placement). For those with high perioperative bleeding risk, antiplatelet agents are stopped 7 to 10 days prior to the procedure.\textsuperscript{6} In these patients, grade 2C recommendations per the ACCP guidelines include re-starting acetylsalicylic acid (ASA) and clopidogrel ~ 24 hours after the procedure in the presence of adequate hemostasis. Again, unfortunately, these recommendations are not based on evidence from the neurosurgical literature, and many neurosurgeons may prefer to withhold antiplatelet therapy until they are comfortable that the patient is at minimal risk for bleeding complications, which typically is on postoperative days 3 to 4 but may be up to 1 week postsurgery. This decision requires a balancing of concerns about thrombotic risk versus bleeding risk and clinical significance of any potential hemorrhage.

Antiplatelet bridging therapy has been proposed in patients at high risk for thromboembolism, as in patients with recent stent placement or myocardial infarction. As these patients may be “bridged” with a short-acting glycoprotein (GP) IIb/IIIa antagonist agent (eptifibatide, tirofiban), it is reasonable to consider re-starting these agents prior to oral antiplatelet therapy. It is important to note that this is an “off-label” use of GPIIb/IIIa agents, and that all decisions with antiplatelet drugs should be made in conjunction with a multidisciplinary team including a cardiologist.\textsuperscript{5} There are no further guidelines concerning other agents, but these agents should not be restarted prior to achieving successful hemostasis. Once they are restarted, the ACCP guidelines recommend against the use of monitoring with platelet function assays.

The use of therapeutic anticoagulation can result in a major bleeding event in up to 10 to 20% of patients.\textsuperscript{4} The decision to restart anticoagulation should incorporate evaluations of intraoperative hemostasis, preoperative thromboembolic risk based on comorbidities, and patient-related factors that may further increase the risk of bleeding (older age, need for concomitant NSAIDs or antiplatelet therapies, impaired renal function, use of spinal/epidural catheter, liver disease, or cancer).\textsuperscript{4} Only after careful consideration of all potential risks for complications can bridging anticoagulation and antiplatelet therapies be resumed.

**Neurosurgery-Specific Issues**

Special consideration must be given to neurosurgical patients in the postoperative period, as they are at high risk for development of potentially life-altering sequelae of both bleeding and development of thromboembolic phenomenon. Minimal literature is available for analysis in this area, and no neurosurgery-specific guidelines have yet been published.

It is well known that agents, such as warfarin, UFH, LMWH, clopidogrel, and ASA, increase the bleeding risk in postoperative neurosurgical patients. Major postoperative bleeding complications may lead to reoperation and possibly the development of permanent neurologic deficits. The most studied and potentially dangerous of these events is the development of an epidural hematoma. The exact incidence of postoperative symptomatic epidural hematoma formation is unknown, but is suspected to be between 0.1% and 1.0% with and without chemoprophylaxis for thromboembolism, and as high as 22% for patients on therapeutic
anticoagulation for preoperative comorbidities.\textsuperscript{7,8} Review of the relevant neurosurgical literature suggests an increased relative risk for epidural hematoma formation with the use of both prophylactic and therapeutic anticoagulants, but the absolute risk of development of this complication is uncertain. That being said, the occurrence may lead to long-term and permanent neurologic deficits. For this reason, numerous neurosurgical-specific recommendations suggest that if anticoagulation is necessary, the use of UFH instead of LMWH is favored as it is more easily controlled, has a shorter duration of action, and is more easily reversed with protamine sulfate.\textsuperscript{9,10}

Venous thromboembolic events after major spinal and intracranial procedures may also complicate recovery of full neurologic function. Patients with a high preoperative thromboembolic risk are at even greater risk for development of thromboembolism resulting from extended recumbency and limited mobility in the postoperative period. Despite these increased risks, restarting antiplatelet and anticoagulation therapy will be primarily dependent on the degree of postoperative hemostasis.

Special consideration can be given to patients bridged for preoperative DVT or PE who have inadequate postoperative hemostasis. These patients should be assessed for temporary inferior vena cava (IVC) filter placement instead of immediate bridging anticoagulant therapy with UFH or LMWH.\textsuperscript{7,8} In patients who have been anticoagulated for atrial fibrillation or mechanical heart valves and who are at increased risk for postoperative development of cerebrovascular accident (stroke or TIA), individual risk-benefit analysis will be necessary to balance initiating or delaying of anticoagulation.

Patients on chronic anticoagulation also present to the neurosurgeon with evidence of intracranial hemorrhage and subdural hematoma from supratherapeutic INR values with or without trauma. Wijdicks et al\textsuperscript{11} addressed in 1998 the question as to how long these patients can be taken off anticoagulation therapy. In patients considered at high thromboembolic risk (prosthetic heart valve with atrial fibrillation, or cage-ball valves), the time off of anticoagulation varied between 2 and 22 days, with no thromboembolic complications. Despite including only nine patients, this retrospective study concluded that for most patients with prosthetic heart valves, cessation of anticoagulation for 1 to 2 weeks is a sufficient amount of time to observe intracranial hemorrhage, clip or coil aneurysms, or evacuate hematoma without an increased risk for development of thromboembolism.\textsuperscript{11}

Patients undergoing elective spine surgery, intervention for traumatic head injury or neoplasm, or patients with intracranial hemorrhage without surgical intervention necessitate particular attention to individualized risk–benefit analysis of a postoperative thromboembolic event and bleeding. These risks must be incorporated into the decision-making process once a patient has achieved adequate hemostasis for reinitiation of anticoagulation. Ultimately, bridging anticoagulation cannot be reinstated until postoperative bleeding is well controlled.

**Case Example 1**

C.K. is a 45-year-old woman who presents to the emergency department (ED) with acute-onset right-sided chest pain. In the past 1 month, the patient has undergone left and right total hip arthroplasty for pathological fractures resulting from lytic bone lesions suspected to be secondary to multiple myeloma. She has been continued on prophylactic doses of Lovenox since after her first surgical intervention.
During evaluation of her chest pain, a computed tomography (CT) angiogram of the chest reveals bilateral, right greater than left, pulmonary emboli. She subsequently has her Lovenox dose increased to therapeutic, twice daily dosing. One week later, the patient again presents to the ED after developing a progressively worsening, diffuse headache, confusion, and slurred speech. A CT of the head indicates an acute intracranial hemorrhage, and the patient undergoes emergent neurosurgical intervention after the anticoagulant effect was emergently reversed. These questions arise: When should anticoagulation be restarted? In the immediate postoperative period, which anticoagulant should be used? The following approach should be considered:

- This patient has a high potential risk for a clinically significant hemorrhage if anticoagulation is restarted too soon but also has a recent DVT and PE diagnosis. A reasonable strategy would be to place a temporary IVC filter and postpone anticoagulant therapy for several weeks, with the filter removal done after therapeutic anticoagulation is achieved.
- In addition to the IVC filter, it may be appropriate to start low-dose heparin therapy at 24 to 48 hours postoperative if the patient’s CT head scan and clinical exam are stable. On postoperative days 2 to 5, the patient should be reassessed to determine if progression of therapy to either low-dose (if not previously started) or high-dose (if already on low-dose) heparin therapy.
- Unfractionated heparin (rather than LMWH) is considered the more appropriate agent for bridging therapy in the neurosurgical patient, as it enables better control of the anticoagulant effect.
- The IVC filter can be removed after the patient has resumed full anticoagulation.

Case Example 2

H.B. is a 72-year-old man with a past medical history significant for type 2 diabetes mellitus, hypertension, stroke, and coronary artery disease, who was initially diagnosed with a stage IIa diffuse large B-cell lymphoma approximately 10 years prior to presentation. The patient received chemotherapy, and was in complete remission after treatment. Eleven months prior to presentation, the patient underwent coronary catheterization, and received a drug-eluting stent to the left anterior descending artery. Since this intervention, the patient has been maintained on clopidogrel. On presentation at a hospital today, the patient’s family reports altered mental status and the patient describes a diffuse, dull headache. CT imaging is significant in showing two lesions in the right temporal and parietal areas suspicious for central nervous system (CNS) lymphoma. The oncology team requests biopsy and plans to consult cardiology for appropriate options for stopping clopidogrel. Assuming cardiology believes that it is appropriate to discontinue clopidogrel for this procedure, and that there were no significant surgical complications, after how many days preoperative should the clopidogrel be stopped and when can it be restarted after the operation? The following approach should be considered:

- Clopidogrel should be stopped 5 to 7 days before the operation.
- Assuming adequate hemostasis, clopidogrel may be restarted at 48 to 96 hours status-postprocedure if the CT head scan and clinical exam are stable.
KEY POINTS

- All intracranial and spine surgeries are considered high bleeding risk procedures.
- No specific evidence-based guidelines exist for postoperative reinitiation of bridging anticoagulation and antiplatelet therapy in neurosurgical patients.
- Patients need to be evaluated on an individual basis for adequate hemostasis and thromboembolic complication risk in the postoperative setting prior to restarting all anticoagulant and antiplatelet therapies.
- The following issues pertain to resumption of anticoagulation in the postoperative setting:
  - All guidelines to date regarding the reinitiation of postoperative anticoagulation and antiplatelet therapy are based on grade 1B/C and 2C recommendations.
  - Preoperative bleeding risk and postoperative hemostasis dictate the timing for starting or restarting anticoagulant and antiplatelet therapy.
  - Preoperative risk of thromboembolism governs the degree of aggression in the dosing of heparin/LMWH postoperatively.
  - If postoperative hemostasis is adequate, UFH/LMWH can be restarted at 48 to 96 hours postprocedure depending on the diagnosis, clinical exam, and CT findings.
  - If postoperative hemostasis is adequate, warfarin can be restarted at 48 to 96 hours postprocedure depending upon the diagnosis, clinical exam, and CT findings.
  - If postoperative hemostasis is adequate, ASA and clopidogrel can be restarted at 48 to 96 hours postprocedure depending on the diagnosis, clinical exam, and CT findings.
  - In patients on ADP receptor inhibitors, GPIIa/IIIb inhibitors, and adenosine reuptake inhibitors, consultation with a cardiologist is recommended prior to restarting these medications.
  - Consider the use of a temporary IVC filter for patients who are at high risk of developing or already have a DVT/PE and have a high risk of bleeding.

REVIEW QUESTIONS

1. Which of the following affect platelet function?
   A. Aspirin
   B. Warfarin
   C. Clopidogrel
   D. Dipyridamole
   E. Heparin

2. True or false?
   A. Patients with an annual thrombotic risk > 2% in the absence of anticoagulation should receive bridging therapy.
   B. Level 1 evidence is available to provide grade A recommendations regarding anticoagulation therapy decisions in neurosurgical patients.
3. True or false?
   A. Preoperative bleeding risk and postoperative hemostasis dictate the timing for starting or restarting anticoagulant and antiplatelet therapy.
   B. If postoperative hemostasis is adequate, warfarin can be restarted at 48 to 96 hours postprocedure depending on the diagnosis, clinical exam, and CT findings.
   C. If postoperative hemostasis is adequate, warfarin can be restarted at 24 hours postprocedure.
   D. If postoperative hemostasis is adequate, UFH/LMWH can be restarted at 24 hours postprocedure.
   E. If postoperative hemostasis is adequate, UFH/LMWH can be restarted at ≥ 48–96 hours postprocedure depending on the diagnosis, clinical exam, and CT findings.

4. True or false?
   A. Preoperative risk of thromboembolism governs the degree of aggression in the dosing of heparin/LMWH postoperatively.
   B. If postoperative hemostasis is adequate, ASA and clopidogrel can be restarted at 24 hours postprocedure.
   C. If postoperative hemostasis is adequate, ASA and clopidogrel can be restarted at 48 to 96 hours postprocedure depending on the diagnosis, clinical exam, and CT findings.
   D. Patients on ADP receptor inhibitors, GPIIa/IIIb inhibitors, and adenosine reuptake inhibitors can restart restarting these medications at 24 hours postprocedure.
   E. In patients on ADP receptor inhibitors, GPIIa/IIIb inhibitors, and adenosine reuptake inhibitors, consultation from a cardiologist is recommended prior to restarting these medications.

5. Regarding inferior vena cava filters, are the following statements true or false?
   A. They are a permanent device.
   B. Anticoagulation is not required when they are used.
   C. They prevent DVT.
   D. They should be considered in patients with a diagnosis of PE and a high risk of bleeding.

References

**ANSWER KEY**

1. A, C, D
2. A: False; B: False; C: True; D: False
3. A: True; B: True; C: False; D: False
4. A: True; B: False; C: True; D: False; E: True
5. A: False; B: False; C: False; D: True
During the initial evaluation of a cranial or spinal lesion, the degree of vascularity should always be considered. Careful assessment of the preoperative neuroimaging and patient history should highlight the possibility of a vascular lesion and significant intraoperative blood loss. If a vascular lesion is included in the differential diagnosis, the neurosurgeon should consider currently available tools for addressing and facilitating hemostasis prior to bringing the patient to the operating room. The primary tool currently available in the preoperative setting is interventional neuroradiology embolization techniques. With the continued development of better X-ray equipment, catheters, wires, and embolic materials, a growing proportion of cranial and spinal lesions are now amenable to embolization. The majority of preoperative embolization procedures utilize a transarterial approach. However, in select cases, percutaneous embolization techniques may also be employed.\(^1\)\(^-\)\(^6\) In addition to reduced intraoperative blood loss, the potential benefits of preoperative embolization include (1) preoperative selective control of surgically inaccessible arterial feeders, (2) reduced operative time, (3) increased probability of complete resection, (4) decreased risk of injury to adjacent neural tissue, (5) possibly reduced lesion recurrence rates, and (6) improved definition of abnormal anatomy and overall visualization of the surgical field.\(^7\)\(^,\)\(^8\)

This chapter provides an overview of the techniques utilized for preoperative embolization and the most commonly employed embolic agents, briefly describes the most common cranial and spinal lesions targeted for preoperative embolization, and discusses important complications and risks to be cognizant of in each case. Importantly, preoperative embolization is only an adjunct to the definitive surgical procedure, and therefore, with each individual case, a risk/benefit analysis must be conducted to ensure that the above-mentioned benefits of embolization outweigh the specific and potentially catastrophic risks of each case.

### Embolization Techniques

**Catheters, Wires, and Technique**

The transarterial embolization procedure can be divided into three stages: an access and diagnostic stage, a selective microcatheter stage, and an embolization stage. Prior to obtaining arterial access, the question of anesthesia must be addressed. Embolization procedures performed on an awake or mildly sedated patient enables continuous neurologic monitoring and provocative testing, while avoiding the risks of general anesthesia (GA). On the other hand, the advantages of GA in-
clude the elimination of patient discomfort and patient movement during critical
diagnostic or embolization portions of the procedure. The main drawback of GA is
the inability to perform real-time neurologic exams. However, neurophysiological
monitoring such as electroencephalography (EEG), somatosensory evoked poten-
tials (SSEPs), and motor evoke potentials (MEPs) can be used as a substitute for a
neurologic exam.9–11 The authors typically perform all intracranial and extracra-
nial head and neck embolization procedures under GA. With spinal embolization
procedures, moderate sedation is sufficient except for cases such as metastatic
thoracic spine lesions that are complicated by patient movement from respiration
or discomfort secondary to the instability pain commonly associated with these
lesions.

Arterial Access

Cannulation of the arterial system typically involves the common femoral artery
but may in certain cases instead entail the brachial, radial, or carotid artery. After
insertion of an arterial sheath, a variety of diagnostic catheters may be advanced to
the appropriate vessel to perform the diagnostic angiogram. The goal of the diag-
nostic stage is to define the general vascular anatomy of the lesions including the
degree of vascularity, arterial supply, and venous drainage. Importantly, the initial
diagnostic angiogram should include a preintervention view of the vascular anat-
omy, which can be used for comparison postintervention. For example, in the case
of extracranial head and neck tumors, this includes performing selective internal
carotid artery (ICA) angiograms so that if there is concern about a thromboem-
bolec complication, a postintervention ICA angiogram can be analyzed for missing
branches or changes in flow.

Catheters (Overview)

After the diagnostic angiogram is performed, the diagnostic catheter is replaced
with a guide catheter. The purpose of the guide catheter is to provide a stable plat-
form for smaller, softer microcatheters to pass through. As a result, these catheters
are usually stiffer and have a larger inner diameter than diagnostic catheters. With
straightforward anatomy, guide catheters can generally be directly re-advanced
into the desired vessel. In the case of tortuous or complex anatomy, the diagnostic
catheter that is already in position can be exchanged for the guide catheter over a
long exchange wire. In some procedures, the diagnostic catheter can be employed
as a guide catheter. In the case of spinal embolizations, the authors commonly use
a 5-French Cobra 2 diagnostic catheter (Merit Medical Systems, Inc., South Jordan,
UT), which has a tip designed to cannulate transversely oriented vessels such as
spinal segmental arteries. The inner diameter is large enough to allow a micro-
catheter through, and the shape of the Cobra 2 catheter tip helps maintain its po-
sition in the segmental artery. The guide catheter is connected to a continuous
heparin saline flush via a rotating hemostatic valve to prevent thrombus within the
catheter but is not sufficient to affect clotting parameters.12 Systemic anticoagula-
tion with heparin is commonly used to reduce thromboembolic complications.13
For embolization procedures, the authors most commonly administer a dose of
heparin 70 IU per kg with a goal of two times the baseline activated clotting time.
Microcatheters and Wires

The next stage of the embolization procedure is the selective microcatheter stage. The goal of this stage is to advance the microcatheter to a position that enables the safe and effective delivery of embolic material to the targeted lesion. The first step of this stage is choosing the appropriate microcatheter. There is a large assortment of microcatheters currently available. The general design of these microcatheters incorporates a stiffer, larger proximal end that tapers into a softer, smaller distal portion. The stiffer, proximal portion enables the catheter to be advanced forward while the more flexible, distal portion enables the catheter to navigate small, distal vessels with decreased risk of vessel rupture or dissection. Microcatheters are braided, which prevents kinking of the catheter when it traverses sharp turns. A hydrophilic coating around the catheter reduces friction between the microcatheter and the guide catheter, and between the microcatheter and the vessel wall. There is some evidence that the hydrophilic coating may reduce the risk of thrombus formation along the catheter.\textsuperscript{14} The general technique of advancing microcatheters is to do so coaxially over a microwire, with the less traumatic wire in front. A special subset of microcatheters that can be advanced in a different manner is the flow-directed microcatheter. The Magic microcatheter (Balt Extrusion, Montmorency, France) and the Marathon microcatheter (ev3, Plymouth, MN) are flow-directed catheters that have extremely soft, small distal tips. With these catheters, the microwire is retracted into the lumen of the catheter while the soft distal tip is carried forward and directed by blood flow, enabling the catheter to be navigated into extremely small vessels with a very low risk of vessel injury. Microcatheter tips may be pre-shaped out of the box or may be custom shaped with steam to facilitate navigation. Lastly, prior to selection of a microcatheter for an embolization procedure, the compatibility with specific embolic materials must be taken into account. The liquid embolic Onyx (ev3, Plymouth, MN) is dissolved in dimethyl sulfoxide (DMSO), and therefore only DMSO-compatible microcatheters such as the Marathon microcatheter can be used. Additionally, particle embolics can aggregate within very small catheters, leading to occlusion and even catheter rupture.

Each microcatheter requires a microwire for navigation, and, similar to the large assortment of microcatheters, there likewise is a large selection of microwires commercially available. Microwire characteristics include size, softness, deformation, steerability, trackability, torque control, and fluoroscopic visibility, which are mainly dependent on the composition of the core wire. Microwires are easily custom-shaped, which is vital for navigating around tight bends and into small distal branches.

Angiography Technique

Biplane fluoroscopy is utilized for navigation cranially, whereas single-plane fluoroscopy is usually sufficient for spinal lesions. To facilitate navigation, the digital roadmap technique is commonly used. With this technique, a mask image of the vascular anatomy is first obtained and then superimposed on real-time fluoroscopic images. The roadmap image is useless if there is patient movement or change in position of the X-ray tube and image intensifier. For that reason, the roadmap technique is not well suited for navigation in the thoracic or lumbar spine because
of respirations and bowel peristalsis. Three-dimensional (3D) roadmap techniques have been developed that utilize the reconstructed 3D image of a rotational angiogram as the roadmap.\textsuperscript{15} The 3D roadmap technique enables the X-ray equipment to be changed to different projections without necessitating acquisition of a new roadmap. Similar to the standard roadmap technique, no patient movement can occur during the acquisition or use of the 3D roadmap.

After reaching the desired microcatheter position, a selective angiogram is performed. Ideally, this position is one in which arterial supply is flowing only to the lesion and from which the selected embolic material can reach the target. In addition to confirming microcatheter position, some other goals of the selective angiogram include ruling out flow to normal brain vessels or a spinal cord artery, and the presence of extra- to intracranial anastomoses in the case of head and neck embolizations. The time needed for interpretation of the selective angiogram is dependent on the target lesion. For example, the evaluation of an intracranial arteriovenous malformation (AVM) requires far greater time than that needed for an L5 renal cell carcinoma metastasis. At this point, provocative neurologic testing can be performed using amobarbital and lidocaine injection. Typically, provocative testing is performed on awake patients and aims to elucidate whether there is blood flow to normal brain, spinal cord, or cranial nerves from the established microcatheter position. It has been demonstrated that provocative testing utilizing EEG can predict neurologic complications after AVM embolization.\textsuperscript{16} An important pitfall of provocative testing is that false negatives can occur as injected drug may be preferentially shunted to high-flow lesions and away from normal neural tissue.\textsuperscript{10,17} Therefore, some authorities argue that detailed analysis of the selective angiogram is as effective as provocative testing in ruling out dangerous anastomoses or filling of normal branches.

### Embolic Agents

There is a broad range of embolic materials currently available for use. During the planning phase of a preoperative embolization procedure, selection of the embolic agent is critical, as it guides the choice of microcatheter and targeted microcatheter position. In selecting an embolic agent, lesion characteristics such as type, location, and rate of flow need to be considered. Embolic agent characteristics that play a factor in the decision include ease of use, cost, and microcatheter compatibility. The discussion in this chapter focus on three categories of embolic agents: particles, liquid embolics, and coils. However, an even wider range of embolic materials has been used in the past and is currently in development.\textsuperscript{18}

### Particle Embolics

Particle embolics are the most commonly used preoperative embolic agents because of the relatively low cost and ease of use. Particle embolics are most effective with lesions that have a capillary bed, such as tumors. One advantage of particles is the ability to deliver the agents from a more proximal microcatheter position because blood flow carries the particles to the tumor capillary bed. The smaller the particle, the more distal it can travel. In the past, particle embolics were used for preoperative embolizations of AVMs, but liquid embolics have largely replaced
them because of the increased risk and more frequent hemorrhagic complications associated with particles.\textsuperscript{19,20} Particles are not radiopaque and therefore must be suspended in dilute contrast to allow for fluoroscopic visualization during injection through the microcatheter.\textsuperscript{21}

The most common particle utilized is the standard polyvinyl alcohol (PVA) particle. PVA particles are irregular in shape and have a tendency to aggregate, which leads to a more proximal occlusion. To minimize the risk of catheter occlusion secondary to particle aggregation, the appropriate-sized microcatheter must be selected and the particle-contrast mixture should not be overly concentrated. Spherical particles such as Bead Block (Terumo Medical Corp., Somerset, NJ), and Embospheres (Merit Medical Systems, Inc., South Jordan, UT) have been designed to have a more consistent shape.\textsuperscript{22} Similarly sized spherical particles tend to travel more distally than standard PVA particles.\textsuperscript{23} Smaller particles are more likely to penetrate the tumor capillary bed and produce a more complete devascularization.\textsuperscript{24} On the other hand, a potential risk of spherical embolic particles or smaller PVA particles (< 150 µm) is passing through fine, distal extra- to intracranial anastomoses during head and neck embolizations, or traveling more distally than intended, which may be associated with an increased risk of postembolization hemorrhage.\textsuperscript{23,25,26} The authors typically use standard PVA particles (150–250 µm or larger in size) in preoperative embolization cases of extra-axial intracranial tumors such as meningiomas, extracranial head and neck tumors, and spinal lesions. With all particles, there is a high probability of recanalization, as the produced occlusion is partly the result of thrombus that is formed around the particles and eventually breaks down. However, when particles are used as a preoperative embolic agent, recanalization is not an important concern because surgical resection is typically undertaken before significant recanalization can occur.

**Liquid Embolic Agents**

Liquid embolic agents have recently been developed that can be easily injected in the liquid state through the microcatheter but polymerize on reaching the bloodstream. The two main liquid embolics that are currently in use are cyanoacrylates ("glue") and Onyx. Of the cyanoacrylates, the most commonly used is n-butyl cyanoacrylate (NBCA) (Trufill, Codman & Shurtleff, Inc., Raynham, MA).

When exposed to an anionic media such as blood, cyanoacrylates rapidly polymerize. The occlusion produced by NBCA is believed to be permanent,\textsuperscript{27–29} but there is some evidence that recanalization of embolized vessels can occur.\textsuperscript{30,31} Meticulous technique must be practiced during preparation and loading of the NBCA to avoid inadvertent polymerization and catheter occlusion. To prevent polymerization in the microcatheter, the catheter is first flushed with 5% dextrose solution. The polymerization time of NBCA can be prolonged by mixing it with ethiodized oil, which is an oil-based contrast agent or glacial acetic acid. Ethiodized oil will also increase the viscosity of the mixture, whereas glacial acetic acid has no effect on the viscosity. Fluoroscopic visualization is further enhanced with the addition of tantalum powder to the mixture. Delivery of the agent can be very tightly controlled, especially if "wedge-flow" is obtained with the microcatheter. In this position the microcatheter tip is occlusive in the distal vessel so that the flow of the delivered agent is directly dependent on each push of the syringe.\textsuperscript{32} A variety of microcatheters can be used with NBCA, including small, flow-directed catheters.
such as the Magic microcatheter. Another advantage of NBCA is the ability to push the embolic agent from a more proximal location because the polymerization time of the glue can be adjusted by changing the ratio of NBCA/ethiodized oil to match the characteristics of the lesion. The major disadvantages of NBCA are a relatively short activation time and the risk of catheter retention due to its strong adhesive properties. In the authors’ practice, the assistant removes the microcatheter immediately after the NBCA injection has ceased in a tightly coordinated manner to minimize the risk of catheter retention. NBCA was initially Food and Drug Administration (FDA) approved for preoperative embolization of AVMs, but it also has been utilized for embolization of other intracranial lesions.33,34

The second liquid embolic, Onyx, is composed of ethylene-vinyl copolymer (EVOH), which is dissolved in DMSO. EVOH precipitates when the solution contacts the aqueous bloodstream and the DMSO disperses. Tantalum powder is added to EVOH and DMSO to enable fluoroscopic visualization. EVOH transforms into a nonadhesive spongy material when it precipitates. Onyx is commercially available with varying percentages of EVOH, which affects the rate of precipitation and distal penetration. Several advantages of Onyx over NBCA include greater ease of use, relatively long activation time, and decreased risk of catheter retention, although this complication may still occur if there is significant reflux. Furthermore, Onyx-occluded vessels are softer than NBCA-glued vessels, which facilitates manipulation during surgery,35 and Onyx penetrates smaller, more distal vessels than NBCA.27 It is believed that Onyx produces less of an inflammatory response as compared with NBCA,36,37 but vascular and perivascular inflammation has been detected in Onyx-embolized, AVM surgical specimens.27 Unlike NBCA, the Onyx injection can be stopped and restarted, which allows the Onyx to be redirected to different vascular compartments of the lesion38 and allows for angiograms during pauses in the injection. Furthermore, if “wedge-flow” is not obtained, an Onyx plug can be formed at the tip of the catheter, which prevents reflux of the agent and confers greater control with each push of the syringe.39,40 The main disadvantages of Onyx are the high cost and the limited set of microcatheters that are DMSO-compatible. DMSO can be toxic to the endothelium if injected too rapidly,38,41 and it produces an unpleasant odor as it is metabolized. There has been some debate about the durability of the occlusion produced by Onyx; in a histopathological study by Natarajan et al,27 recanalization was observed in 18% of resected AVM specimens. Similar to NBCA, Onyx was initially FDA approved for the embolization of AVMs, but its use has expanded to other cranial lesions.4,42,43

**Microcoils**

Microcoils are platinum coils of varying sizes and shapes that can be advanced into a targeted vessel through a microcatheter. In the case of preoperative embolizations, coils are typically utilized as a supplement to other embolic agents by further decreasing flow from an arterial feeder and reducing the rate of recanalization after particle embolization of the tumor capillary bed. Additionally, during extracranial embolizations, microcoils can be deployed to redirect particle embolics to a targeted lesion when the microcatheter cannot be advanced distally or selectively enough to protect normal territory or a dangerous anastomosis. Pushable coils are platinum coils that have interweaving thrombogenic fibers composed of nylon, polyester, or other synthetic substance. The coils require larger-diameter
microcatheters and are advanced with a coil pusher. The most common class of coils used in interventional neuroradiology is the detachable platinum coil, which was initially designed and still primarily used for the embolization of intracranial aneurysms.\textsuperscript{44,45} The prototype coil is the Guglielmi detachable coil (GDC; Boston Scientific Corp., Natick, MA). Detachable coils remain attached to the coil pusher until electrically or mechanically released by the operator and therefore may be repositioned as needed or removed altogether. A significant disadvantage of detachable platinum coils is the high cost.

**Direct Tumor Puncture Embolization**

In addition to transarterial embolization, percutaneous embolization techniques have been described as a method to devascularize lesions preoperatively. The most common embolic agents utilized with this technique include the liquid embolics NBCA and Onyx. These techniques have been described for head and neck tumors such as paragangliomas, juvenile nasal angiofibromas, and hemangiopericytomas of the calvarium.\textsuperscript{1–5,46} Schirmer et al\textsuperscript{6} described the percutaneous injection of NBCA in a series of five patients with highly vascular, renal cell carcinoma spinal metastases as a complement to transarterial embolization. Percutaneous direct tumor embolization can still carry the risk of ischemic complications, as the embolic material may reflux into branches supplying cranial nerves, branches with extra- to intracranial anastomoses, or reflux directly into the intracranial circulation.\textsuperscript{47–49} To reduce the risk of emboli traveling into the intracranial circulation, angiography is performed in conjunction with the direct head and neck tumor puncture, which helps guide the degree of embolization, and balloon catheters can be placed in the ICA or vertebral artery as a protective measure.

**Timing of Surgery**

The optimal timing of surgery for tumor resection after preoperative embolization has been debated. One group of neurointerventionists and neurosurgeons has recommended delayed surgery, typically 1 to 2 weeks following embolization. The argument is that the delay allows for embolization-induced tumor necrosis and resulting softening of the tumor, with one study, by Kai et al,\textsuperscript{50} concluding that maximum tumor resectability was achieved 7 to 9 days after embolization. On the other hand, other authors have recommended early surgical resection following preoperative embolization.\textsuperscript{51,52} The disadvantage of delayed surgery is the risk of tumor edema and hemorrhage that may occur during the days following embolization.\textsuperscript{26,52,53} However, at least 24 hours should elapse after embolization for the best hemostatic effect as demonstrated by Chun et al\textsuperscript{54} in a series of embolized meningiomas. Dexamethasone is usually administered periprocedurally to reduce embolization-induced tumor edema. Another potential disadvantage of delayed surgery is the risk of misgrading tumors. For example, meningiomas may be overgraded because of embolization–induced necrosis and reactive changes.\textsuperscript{55–57} The authors typically perform preoperative cranial and spinal tumor embolization 24 to 48 hours prior to the scheduled surgery. In the case of AVMs, surgical resection is usually performed 3 to 30 days after the last stage of embolization.
Common Preoperatively Embolized Lesions

Cranial, Head, and Neck Lesions

Meningiomas

One of the most common tumors for which preoperative embolization is performed is meningiomas. These lesions, arising from arachnoid granulation cells, are one of the most common primary central nervous system (CNS) tumors. Frequently observed locations include the parasagittal and falcine region, cerebral convexities, sphenoid wing, parasellar region, olfactory groove, and tentorium. Multiple meningiomas are present in about 8% of patients.

As the tumors arise from the arachnoid, meningeal branches of the external carotid artery (ECA) are usually the initial blood supply, though the tumors may recruit pial vessels. The middle meningeal artery (MMA) most commonly supplies tumors overlying the cerebral convexities, parasagittal region, and sphenoid wing. The supply may be from bilateral MMA when the tumor location is parasagittal or crosses the midline. In the case of olfactory groove meningiomas, feeders usually arise from dural branches of the ICA that include the ethmoidal branches of the ophthalmic artery. Tentorial or clival meningiomas may receive supply from cavernous ICA branches such as the artery of Bernasconi and Cassinari. Posteromedial posterior fossa meningiomas usually receive supply from meningeal branches of the vertebral artery, whereas more lateral lesions may receive supply from the occipital artery or the ascending pharyngeal artery (APA).

In general, the target of embolization procedures is the ECA tumor feeders because of the increased stroke risk associated with the embolization of ICA feeders. There is variability in the degree of vascularity and therefore the intensity of the tumor blush. A “spokewheel” pattern of intratumoral vessels may be observed. The diagnostic angiogram also provides important information regarding the patency of dural sinuses such as the superior sagittal sinus especially in the case of parasagittal and falcine meningiomas. For large, highly vascular lesions, preoperative embolization may reduce intraoperative blood loss. However, there have been only a handful of comparative studies demonstrating this benefit. Dean et al published a retrospective analysis of 18 embolized patients with meningiomas that were matched with 18 nonembolized patients. The authors found that patients with preoperatively embolized tumors had statistically significantly decreased intraoperative blood loss and transfusion requirements. Another study compared the results at two different neurosurgical centers. One group of neurosurgeons regularly employed preoperative embolization and the other group did not. Intraoperative blood loss was significantly reduced when a greater than 90% devascularization was achieved during embolization.

The most commonly employed embolic material is particle embolics such as PVA, but liquid embolics such NBCA and Onyx have also been used. Importantly, with all ECA embolizations, an understanding of possible extra- to intracranial anastomoses and cranial nerve supply must be attained. An ischemic neurologic complication rate of around 3% has been reported and can occur secondary to emboli traveling to unrecognized extra- to intracranial anastomoses or reflux of material into branches with anastomoses or supply to normal neural tissue. Hemorrhagic complications may also occur and are likely secondary to the increased fragility of tumor vessels after tumor necrosis or the result of venous outflow obstruction due to particles traveling too distal.
Hemangiopericytomas

Intracranial hemangiopericytomas or meningeal hemangiopericytomas are relatively uncommon tumors, occurring at a frequency of 2.4% of meningiomas.\textsuperscript{67} The lesions are thought to arise from pericytes, which are the contractile cells surrounding capillaries. The lesions are found most commonly in the supratentorial compartment but do occur in the posterior fossa. The lesions tend to be highly vascularized with prominent vessels often visualized on magnetic resonance imaging (MRI).\textsuperscript{68}

The diagnostic angiogram usually exhibits a prolonged, intense, heterogeneous tumor blush with “corkscrew” vessels.\textsuperscript{69,70} There is often a mixed dural–pial vascular supply to the tumors.\textsuperscript{70} Because of the significant vascularity and dual vascular supply, significant intraoperative blood loss is often observed.\textsuperscript{67,71–73} For that reason, preoperative embolization is advocated. In a small series by Fountas et al,\textsuperscript{72} the average blood loss from embolized tumors was 508 mL versus 1,160 mL for nonembolized tumors. Targeted tumor feeders include both ICA and ECA branches that can be super-selectively catheterized. The use of embolic materials such as PVA particles, detachable coils, and NBCA have been reported in the literature.\textsuperscript{33,74,75} Given the rarity of these lesions, no large comparative study has been published definitively demonstrating the hemostatic benefit of preoperative embolization. However, most authors strongly recommend preoperative embolization if possible.\textsuperscript{72,74,76}

Hemangioblastomas

Hemangioblastomas comprise a small percentage of all primary CNS neoplasms but comprise 7 to 12% of primary posterior fossa tumors,\textsuperscript{77} and are the most common primary intra-axial posterior fossa tumor in adults. The classic description of hemangioblastoma is a cystic mass with a mural nodule, though a considerable percentage of the tumors are solid.\textsuperscript{78} The majority of the lesions are sporadic but about 10 to 20% are associated with von Hippel–Lindau disease. The most common location is the cerebellum, with a much smaller proportion in the medulla and in the intramedullary compartment of the spinal cord.\textsuperscript{79}

In addition to the cyst and mural nodule, serpentine flow voids are often visualized on MRI.\textsuperscript{78} On diagnostic angiogram, a small highly vascular mural nodule is typically observed with a prolonged vascular stain.\textsuperscript{80} Because of the significant vascularity, massive intraoperative blood loss is a recognized danger during surgical resection.\textsuperscript{81} To improve intraoperative hemostasis, preoperative embolization has been recommended by many authors for resection of both cranial and spinal lesions.\textsuperscript{53,81–84} However, because of the small number of cases, no systematic comparative analysis of the benefits of preoperative embolization has been published. The literature to date has primarily described the use of particle embolics for preoperative embolization.\textsuperscript{23,53,82,84} Intra-procedure and postprocedure tumor hemorrhage after particle embolization is a significant documented complication.\textsuperscript{23,85} In addition to tumor hemorrhage, tumor edema is possible,\textsuperscript{53,82} and ischemic complications may occur from inadvertent occlusion of branches that fill normal cerebellar brain tissue.\textsuperscript{86} With the development of liquid embolics such as NBCA and Onyx, more effective and safer preoperative embolizations may possibly be undertaken.\textsuperscript{4,33,87,88}
Choroid Plexus Tumors

Choroid plexus tumors include choroid plexus papillomas and carcinomas, of which papillomas are twice as common as carcinomas. The tumors may occur at any age, but 70% of the patients are younger than 2 years old. Choroid plexus tumors are rare, but in children younger than 2 years old they may account for up to 12% of intracranial tumors. In pediatric cases, the tumors are usually located in the lateral ventricle, but in adults the lesions are typically found in the fourth ventricle. The lesions may have significant vascularity, and surgical mortality attributed to intraoperative blood loss may be as high as 12%.

In the past, preoperative embolization was hampered by the lack of microcatheters capable of cannulating the small choroidal vessels that feed the tumors. With the development of small, flow-directed microcatheters such as the Magic and Marathon microcatheters, cannulation of these vessels is now possible. Various embolic materials have been utilized for embolization, including PVA particles, Onyx, and NBCA. At this time, no large comparative study has been published quantitating the benefit of preoperative embolization because of the limited number of cases.

Paragangliomas

Paragangliomas or glomus tumors of the head and neck arise from chemoreceptor cells of the paraganglia or glomus bodies. The most common locations are the carotid body, middle ear, jugular fossa, vagus nerve, and larynx. The lesions are slow-growing and locally invasive, leading to bony destruction and infiltration of adjacent structures. The classic description on MRI is a “salt-and-pepper” appearance on T1 or T2 sequences, which represent high velocity flow voids within the tumor.

Diagnostic angiogram demonstrates a dense vascular blush, with frequent ECA feeders from branches of the APA and occipital artery as well as the MMA. In some instances, supply may also arise from the ICA or vertebral artery. Given the vascularity of the lesions, many authorities advocate preoperative embolization of major ECA feeders prior to surgical resection. The most commonly used embolic material is PVA particles. Tikkakoski et al described their experience with preoperative embolization of neck paragangliomas in 20 patients. In nine preoperatively embolized patients, the intraoperative blood loss averaged 588 mL versus an average of 1374 mL in 11 nonembolized patients. In the case of carotid body tumors, there is some evidence that preoperative embolization does not significantly alter intraoperative blood loss, and therefore some authors do not recommend embolization in these cases. However, analysis of nationwide inpatient data for treated carotid body glomus tumors demonstrated that preoperative embolization was associated with fewer blood product transfusions. In addition to transarterial embolization techniques, direct tumor embolization of paragangliomas has been performed with success as described in the previous section. The most commonly used embolic materials include PVA particles and liquid embolics such as NBCA and Onyx.

Possible complications of embolization include ischemic stroke and cranial nerve palsies secondary to branch occlusion or tumor edema. The occurrence of cranial nerve palsies is likely due to the fact that commonly targeted ECA branches such as the neuromeningeal trunk of the APA provide arterial supply to the lower cranial nerves. The risk of permanent cranial nerve palsy is reduced with the use
of reabsorbable embolic materials or particles larger than 150 µm. Lastly, extra- to intracranial anastomoses must be ruled out to prevent an inadvertent shower of emboli into the ICA or vertebral artery.

**Arteriovenous Malformations**

Arteriovenous malformations are rare congenital CNS lesions that are part of the spectrum of intracranial vascular malformations. These lesions are high-flow shunts between intracranial arterial feeders and enlarged deep or superficial veins, connected by a nidus of abnormal, malformed vessels. Gliotic, hemosiderin-stained brain parenchyma is found around the AVM nidus. The risk of an initial hemorrhage is 2 to 4% per year.\(^ {109-114} \)

The role of embolization in the treatment of AVMs has evolved over time for these complex lesions. As a stand-alone curative procedure, endovascular embolization at this time is only appropriate for a small subset of AVMs.\(^ {115} \) Currently, endovascular embolization is combined with microsurgical resection or radiosurgery in a multimodality treatment approach.\(^ {116-119} \) The primary target of AVM embolization is the nidus, though features such as flow-related and intranidal aneurysms warrant special attention during the preoperative embolization.\(^ {120} \) For AVMs, preoperative embolization may reduce intraoperative blood loss by occluding deep, surgically difficult-to-reach arterial feeders, reducing nidus size, and reducing flow and degree of arteriovenous (AV) shunting. Other advantages of preoperative embolization include reduced operative time and decreased risk of perioperative rupture of intranidal aneurysms or flow-related aneurysms.\(^ {121} \)

The diagnostic stage and selective microcatheter stage of the preoperative AVM embolization require careful examination. The angiographic analysis of the arterial feeders includes defining true terminal feeders from en passage vessels or pseudoterminal vessels, arteriopathy such as stenoses or ectasias, and flow-related aneurysms. Analysis of the AVM nidus includes defining the size, shape, location, rate of flow, ectasias, and intranidal aneurysms. Lastly, angiographic analysis of the venous drainage includes understanding the deep or superficial pattern, the number of draining veins, the specific veins and territories, the dural sinuses involved, stenoses, occlusions, and varices.\(^ {122} \)

The PVA particles have been largely replaced by the liquid embolics NBCA and Onyx, which were given FDA approval for AVM embolization in 2000 and 2005, respectively. After PVA embolization, there was a higher rate of postresection hemorrhage compared with patients who underwent preoperative embolization with NBCA.\(^ {19} \) Despite the above-stated theoretical advantages of preoperative AVM embolization, there are few comparative studies definitively demonstrating decreased intraoperative blood loss after preoperative AVM embolization. Pasqualin et al\(^ {123} \) found that there was reduced intraoperative bleeding in patients with preoperatively embolized AVMs when the lesion was greater than 20 mL in volume. The embolic agents utilized in the study were Silastic sponge and polyfilament polyethylene thread since the study was performed prior to the routine use of liquid embolics. Jafar et al\(^ {124} \) demonstrated in a group of 33 patients who underwent surgery alone or combined with NBCA, intraoperative blood loss was similar despite the fact that the AVMs in the embolized group were significantly larger and were of a higher Spetzler-Martin grade. Intraoperative blood loss has not been shown to be significantly different between NBCA-embolized AVMs versus PVA-embolized AVMs,\(^ {19} \) or between NBCA-embolized AVMs versus Onyx-embolized AVMs.\(^ {37} \) Multi-stage embolizations can be performed prior to surgical resection. The authors typ-
Managem ent of Bleeding and Coagulation

cially wait 2 to 4 weeks between each stage of embolization. Complications associated with AVM embolizations are not insignificant and include periprocedural hemorrhage, ischemic events, and death. Several recent series have reported mortality rates between 1% and 2.6% and permanent disabling complication rates between 1.6% and 11%. Complications related to the embolization procedure may be limited by careful evaluation of the superselective angiogram, use of less traumatic flow-directed catheters, use of liquid embolics, tight periprocedural blood pressure management, and staged embolizations that may reduce the incidence of periprocedural hemorrhage secondary to normal perfusion pressure breakthrough.

Spinal Lesions

Metastatic Spine Disease

Hypervascular metastatic disease of the spine most often involves renal cell, thyroid, breast, prostate, lung, and hepatocellular carcinomas as well as melanoma. Metastatic tumors present with metastases to the spine in 30 to 70% of cases. Of the above-mentioned tumors, renal cell carcinoma (RCC) and thyroid carcinoma are the most commonly associated with highly vascularized vertebral body lesions, and the majority of the literature demonstrating the benefits of preoperative embolization has focused on RCC. As a result of the significant vascularity, surgical resection of these metastatic spinal lesions is hampered by the extensive intraoperative blood loss, which results in increased morbidity and mortality.

Preoperative embolization has been strongly advocated as a critical component of the treatment paradigm for hypervascular metastatic spine disease. A study by Berkefeld et al, which predominantly involved patients with RCC, reported average intraoperative blood loss in nonembolized patients of 4,350 mL versus 1,800 mL in patients who underwent PVA particle embolization. The investigators also combined coils with PVA particles in select cases, but the coils did not appear to confer additional hemostatic benefit. In another small study of 17 patients with preoperatively embolized RCC spinal metastases and 10 matched controls, the hemostatic benefit of PVA particle embolization was also demonstrated. In fact, for two of the control patients, the resection was aborted because of life-threatening hemorrhage. In a recent report by Wilson et al of 100 spinal preoperative embolizations for both primary and metastatic tumors, RCC accounted for 38% of the cases. The authors found that RCC was associated with significantly increased intraoperative blood loss as compared with the other pathologies. A benefit from preoperative embolization was confirmed in that the average intraoperative blood loss for partially or nonembolized RCC tumors was 3,460 mL versus 1,821 mL for completely embolized RCC tumors. Additionally, adjunctive percutaneous embolization techniques have been described for the embolization of RCC spinal metastases as mentioned previously.

Camille et al were the first to report on the use of preoperative embolization of spine and pelvic thyroid carcinoma metastases. However, no large series or comparative study has been published to date demonstrating the efficacy of preoperative embolization for thyroid carcinoma metastases.

A major possible neurologic complication related to the embolization procedure is spinal cord ischemia secondary to occlusion of a radiculomedullary branch.
that fills a spinal cord artery. This can be avoided through careful examination of the segmental artery angiogram.\textsuperscript{139} In the case of cervical spine tumors, the interventionist must be vigilant for possible anastomoses between the carotid, vertebral, and costocervical, and thyrocervical trunks of the subclavian artery, which can result in cerebral emboli and infarction.\textsuperscript{138,144,145}

**Primary Spine Bony Lesions**

Preoperative embolization has been utilized in the treatment of primary bone tumors such as hemangiomas, osteoblastomas, aneurysmal bone cysts, and giant cell tumors. Hemangiomas are common benign lesions of the vertebral body that can produce spinal cord compression from mass effect or pathological compression fracture.\textsuperscript{146} Preoperative embolization has been recommended by various authors because of the potential for significant intraoperative blood loss.\textsuperscript{147–149} Symptomatic spinal hemangiomas may benefit from transarterial preoperative embolization with particle embolics or Onyx prior to undergoing surgical resection.\textsuperscript{150,151} Osteoblastomas account for about 3% of benign and 1% of all primary bone tumors.\textsuperscript{152} Surgical resection is the treatment of choice\textsuperscript{153}; however, complete surgical excision is usually impeded by excessive intraoperative bleeding. In a small series by Trübenbach et al,\textsuperscript{154} preoperative embolization with particle embolics was accomplished in three cases of cervical spine osteoblastoma with no reported complications. The authors did not specify the exact degree of blood loss in these cases. Aneurysmal bone cysts are expansile bone lesions that are characterized by a reactive proliferation of connective tissue and multiple blood filled cavities.\textsuperscript{155} Preoperative embolization with PVA particles is utilized for these highly vascular lesions in an attempt to prevent excessive intraoperative bleeding.\textsuperscript{147,155,156} However, aneurysmal bone cysts usually lack a true major feeding vessel and are supplied instead by a network of small vessels, which makes preoperative embolization unfeasible in some cases.\textsuperscript{147}

As is the case for embolizations of metastatic spine lesions, avoidance of neurologic complications involves careful examination of the preintervention diagnostic angiogram to identify the presence of any radiculomedullary branches that fill spinal cord arteries and the presence of any anastomoses to the carotid or vertebral arteries in the case of cervical spine lesions.

**Conclusion**

There is a variety of hypervascular benign and malignant lesions in the craniospinal axis for which surgical resection may be significantly hampered by excessive intraoperative blood loss. The extensive blood loss that may occur in these cases can lead to significant morbidity and mortality. The development of new technologies and materials such as digital 3D roadmapping, flow-directed microcatheters, and liquid embolic agents has allowed neurointerventionists to address more and more of these hypervascular lesions prior to attempted surgical resection. Embolization procedures do carry risks, and those risks must be carefully weighed against the morbidity and mortality associated with surgical resection without preoperative embolization. However, all practicing neurosurgeons should be aware of this growing armamentarium now available for attaining preoperative preemptive surgical hemostasis of hypervascular lesions.
KEY POINTS

• Careful attention should be paid to the preoperative imaging to determine if the lesion to be removed would be appropriate for endovascular treatment to reduce blood loss at surgery.
• The use of microcatheters for selective embolization facilitates safety with preoperative embolization.
• Agents for tumor and vascular malformation embolization include particles, liquid embolics, and coils.
• Onyx, a liquid embolic agent, has been a revolutionary improvement in the endovascular armamentarium.
• For AVMs, liquid embolic agents have superseded the use of particles for embolization.
• Timing of surgery should be carefully planned when using particles to avoid recanalization of the vascular supply.

REVIEW QUESTIONS

1. The advantages of Onyx over NBCA include:
   A. Less expensive to use
   B. Longer working time
   C. Rapid setting
   D. DMSO solvent
   E. None of the above

2. Which embolization agent is most likely to develop recanalization over time?
   A. Coils
   B. Onyx
   C. NBCA
   D. PVA

3. The most common cranial tumors in which embolization is used prior to surgery is:
   A. Glioma
   B. Hemangioblastoma
   C. Hemangiopericytoma
   D. Meningioma
   E. Metastasis

4. True or False: Tentorial meningiomas usually receive arterial supply from the external carotid artery.

5. Spine lesions amenable to preoperative embolization include:
   A. Vascular metastases
   B. Hemangioma
   C. Aneurysmal bone cyst
   D. Osteoblastoma
   E. All of the above
6. The major risk of embolization of spine lesion is
   A. Possible aneurysmal bone cyst (ABC)
   B. Spinal cord ischemia from occlusion of a radiculomedullary branch that fills a spinal cord artery
   C. Spinal level of the lesion
   D. Type of tumor
   E. Use of coil and particles in combination

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117. Natarajan SK, Ghodke B, Britz GW, Born DE, Sekhar LN. Multimodality treatment of brain arteriovenous malformations with microsurgery after embolization with onyx:


**ANSWER KEY**

1. B
2. D
3. D
4. False
5. E
6. B
Intraoperative Non-Hematologic Adjuvant Methods for Preventing Blood Loss
Ian Y. Lee, Raymond Sawaya, and Nicholas B. Levine

Hemostatic techniques, including metal clips, mechanical tamponade, and ligation, used in other forms of surgery have some utility in neurosurgery; however, the delicate and friable nature of neural tissues has led to the development of other hemostatic techniques. Meticulous hemostasis must be adhered to because of surgeons’ general intolerance for blood accumulation while they are working in a small surgical cavity, intracranially or in the spine. In general, there is a lack of basic understanding about how to use these agents, even among practitioners, as there is a paucity of studies that address this topic specifically. Thorough understanding of the mechanisms of action and of the advantages and disadvantages of the various materials and techniques available is crucial for safe and efficacious surgery. This chapter discusses some of the chemical, electrical, thermal, and adjuvative methods for hemostasis in use in neurosurgery today.

General Historic Overview

The first descriptions of hemostasis date back to ancient Egypt, where descriptions of thermal cautery have been found, ranging from the use of hot irons and stones to boiling oil. Described by Galen, this was the preferred method of hemostasis for most of antiquity. Although effective, using conductive heat to induce hemostasis caused damage to the surrounding tissues. The advantage of this technique was that it worked quickly and effectively, which was certainly a necessity in times when anesthetics and asepsis were not available.

In the 1500s, Ambroise Paré pioneered the use of ligature for hemostasis rather than cauterization during amputation. To achieve this, he designed and used the “bec de corbin,” a predecessor of the modern hemostat. Sterilization and aseptic technique had not been developed, and therefore, the use of ligature often led to the spread of infection. However, this was a breakthrough, and it remains a mainstay of modern surgical technique.

In the 1920s, a milestone in hemostasis was achieved with the invention of monopolar electrocautery by William T. Bovie and Harvey Cushing. By using induction rather than conduction to transfer heat to tissues, the area of heat generation could be more finely controlled. First used in 1926 in an operation, by Cushing, this predecessor to modern monopolar electrocautery is still the most widely used method to achieve hemostasis in surgery.

Descriptions of chemical hemostasis with styptics and caustics can be found in the Hippocratic Corpus. Styptics, substances that induce vasoconstriction, date back to the early Greeks and Romans, who used vegetable and mineral styptics for the treatment of battle wounds. In the Middle Ages, copper sulfate was used as a caustic. Caustics produced hemostasis by denaturing proteins indiscriminately, with
uncertain and unreliable quality. Still, the use of caustic substances remained popular until the introduction of ligature. The advantage of chemical caustics was that they could be used on capillary bleeding, too small for ligatures. As technology advanced, less reactive and destructive substances have been developed.

Mechanical hemostasis, an effective technique for stopping surgical and traumatic bleeding, dates back to the Romans, who used straps of bronze and leather as tourniquets to reduce bleeding during amputations. Before the advent of microsurgery and bipolar coagulation, neurosurgeons would have to stop frequently to apply pressure via cotton packs to stop bleeding, thus leading to long surgical times. The tissues had a tendency to rebleed once the packs were removed. To avoid rebleeding, Cushing used skeletal muscle instead of cotton packs to induce mechanical hemostasis. The muscle could be left permanently; however, the use of muscle was discontinued due to unacceptable tissue reactions. With the introduction of gelatin sponges, mechanical hemostasis continues to be widely used in neurosurgery even today.

**Table 17.1 Description of Hemostatic Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade Names</th>
<th>How Supplied</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin sponge</td>
<td>Gelfoam, Surgifoam, Spongostan, Floseal</td>
<td>Sheet, Powder</td>
<td>Mechanical</td>
</tr>
<tr>
<td>Oxidized cellulose</td>
<td>Surgicel (Fibrillar, Nuknit, SNoW), Oxycel</td>
<td>Pads, Strips, Powder</td>
<td>Chemical, Mechanical</td>
</tr>
<tr>
<td>Microcrystalline collagen</td>
<td>Avitene</td>
<td>Powder</td>
<td>Chemical, Mechanical</td>
</tr>
<tr>
<td>Thrombin</td>
<td>Thrombin-JMI</td>
<td>Powder</td>
<td>Chemical</td>
</tr>
<tr>
<td>Fibrin glue</td>
<td>Tisseel, Evicel, Artiss, Beriplast, Tissucol</td>
<td>Spray, Double-barrel syringe</td>
<td>Chemical</td>
</tr>
<tr>
<td>Bone wax</td>
<td>Bone Wax, Ostene</td>
<td>Wax</td>
<td>Mechanical</td>
</tr>
</tbody>
</table>
As technology and techniques have advanced, hemostatic agents have been introduced that are more selective and less traumatic. The techniques of hemostasis have remained constant; the options are chemical, mechanical, or thermal/electrical. This chapter describes the materials and tools available to neurosurgeons today.

### Absorbable Gelatin Sponge (Gelfoam, Surgifoam)

First used in 1945, Gelfoam (Upjohn, Kalamazoo, MI) and Surgifoam (Ethicon, New Brunswick, NJ) (Table 17.1) are water-insoluble absorbable sponges prepared from purified porcine skin gelatin. The hemostatic properties are primarily due to mechanical hemostasis, as it is capable of absorbing up to 45 times its weight of whole blood.\(^7\) It may also act as a supportive structure, producing a matrix that facilitates clotting as well as forming an artificial clot.\(^8\) It has been proposed that platelets

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonantigenic</td>
<td>No intrinsic hemostatic properties</td>
<td>Can be combined with thrombin</td>
</tr>
<tr>
<td>Absorbs large amounts of blood</td>
<td>Foreign body, infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Swells, can compress adjacent structures</td>
<td></td>
</tr>
</tbody>
</table>

| Bacteriocidal | Foreign body, infection | Interferes with hemostatic properties of other agents due to low pH |
| Mild tissue reaction | Swells, compressive neuropathy | |
| Rapid absorption | Interferes with bone healing | |
| Easy handling | Can cause narrowing of blood vessels | |

| Small amount necessary | Tends to float off briskly bleeding surfaces | Good for dural sinus bleeding |
| Easy to remove without risk of rebleeding | Foreign body, infection | Can be used as wafer or “sandwich” |
| Does not interfere with bone healing | | |

| Works quickly | Antigenic | Can be combined with gelatin sponge |
| Can be used in heparinized patients | Not suitable for arterial bleeding | |

| Works quickly | Antigenic | Also used as dural sealant, peripheral nerve repair |
| Can be used in heparinized patients | Can be difficult to use | |
| Mild tissue reaction | | |
| Not dependent on host factors | | |

| Most effective for bone bleeding | Not reabsorbed | Ostene is absorbable, does not interfere with bony healing |
| Does not wash off | Interferes with bony healing | |
| Easy to use | Foreign body, causes inflammatory reaction, serve as nidus for infection | |
enter the sponge, then release thromboplastin after being activated by contact with the walls of the interstices of the sponge. The thromboplastin then reacts with calcium and prothrombin, causing the production of thrombin, thus initiating the clotting cascade.9

The gelatin sponge may be used alone or soaked with saline, but is often soaked with thrombin (Pfizer, New York, NY), thereby supplementing its mechanical hemostatic properties with the chemical hemostatic properties of thrombin. If used in concert with thrombin, excess thrombin should be removed from the gelatin sponge. The sponge is applied directly to the bleeding surface. A cotton pledget is then applied on top of the sponge and held for at least 10 seconds, whereupon the pledget may usually be removed. To achieve maximum utility, blood should be allowed to soak to the outer surface of the sponge. The gelatin sponge may also be cut to a smaller thickness, and may be sliced as small as 2 mm without fragmenting. The thinnest effective sponge should be used to achieve hemostasis, as Gelfoam swells tremendously.10

A principal disadvantage of the gelatin sponge is its tendency to leak plasma after clot formation.11 In addition, because of its capacity to swell, compression of neural structures can result. There have been multiple case reports of symptomatic compression of brain and spinal structures, including cauda equina syndrome, stenosis, and paresthesias.12 Although Gelfoam is thought to be relatively nonreactive, there have been case reports of giant-cell granuloma formation at the implantation site.13

The time to absorption depends on several factors, including the site used, saturation with bodily fluid, and the amount used. By 4 to 6 weeks after implantation into soft tissues, the gelatin sponge is usually completely absorbed.9,14–16 By contrast, when used on bleeding nasal, rectal, or vaginal mucosa, it has been observed to liquefy within 2 to 5 days. The cellular reaction observed has been reported to be similar to that of natural clot resorption and does not seem to cause excessive scar formation.15 Still, it should not be used in the closure of skin incisions, as the gelatin sponge may interfere with the healing of skin edges due to the interposition of the sponge between the tissue surfaces. In addition, Gelfoam should not be used with autologous blood salvage circuits, as it may theoretically result in disseminated intravascular coagulation.17

Although non-antigenic, the gelatin sponge is still a foreign body, and thus may serve as a nidus for infection. Several studies have shown increased infection, especially when used in contaminated fields.18–19 Consequently, the minimum amount of gelatin sponge should be used if it will potentially be left in the surgical field. Additionally, mixing antibiotic sponges with the gelatin sponge is not recommended.

The gelatin sponge is also available in a variety of forms. Gelfoam Plus (Baxter, Deerfield, IL) is a Gelfoam sponge that comes prepackaged with thrombin. It is also available in powder form mixed with thrombin (Floseal, Baxter Deerfield, IL; Surgiflo, Ethicon, New Brunswick, NJ), which is particularly useful for cancellous bone bleeding.

Oxidized Cellulose (Oxicel) and Oxidized Regenerated Cellulose (Surgicel)

There are two commercially available forms of oxidized cellulose: oxidized cellulose (Oxycel, Becton Dickinson, Sandy, UT) and regenerated oxidized cellulose (Surgicel,
Intraoperative Non-Hematologic Adjuvant Methods

Ethicon, New Brunswick, NJ). Both are available in a variety of forms and preparations including pads, strips, and powder. Oxidized cellulose consists of cellulose that is subjected to oxidation by nitrous oxide. This oxidation causes conversion of hydroxyl radicals on the cellulose to become carboxyl groups, leading to a functional unit consisting of anhydroglucuronic acid. Surgicel, regenerated oxidized cellulose, is a similar material, but made by a different process. It is formed by dissolving the pure \( \alpha \)-cellulose in an alkali solution. It is then extruded as a continuous fiber, knitted into gauze, and oxidized. The resultant fabric is thus more uniform in composition as well as the oxidation more closely regulated. Consequently, this results in less variation of the product in terms of absorbability and tissue reaction. Both agents are similar with respect to hemostatic properties.

Both products were developed in the 1940s, when it was observed that oxidized cellulose facilitated hemostasis. It was first thought that the hemostatic properties were purely due to mechanical effects. It was proposed that the oxidized cellulose acted as a physical matrix that platelets adhered to, thus leading to artificial clot formation. It was later discovered that there was some contribution due to its caustic characteristics. When oxidized cellulose encounters blood, it reacts with it to form a reddish gelatinous mass containing hematin (which accounts for the color change to reddish-black). In contrast to the gelatin sponge, oxidized cellulose relies more on its chemical hemostatic properties than on mechanical properties.

Because of the oxidation of the cellulose, the resultant fabric has a very low pH. It is best used alone. The addition of saline or thrombin can decrease its effectiveness. Thrombin is denatured when it comes into contact with the low pH of the oxidized cellulose, thus destroying its chemical hemostatic properties. Additionally, due to its low pH, oxidized cellulose has some bacteriostatic properties, thus denaturing some bacterial proteins and making them more susceptible to antibiotics. Oxidized cellulose has been found to have activity against a wide variety of bacterial pathogens. In a comparison of artificially inoculated wounds, oxidized cellulose was found to have a significantly lower rate of infection compared with Gelfoam and microfibrillary collagen, although a higher rate than in the control population. This suggests that the use of oxidized cellulose can partially ameliorate the tendency of foreign bodies to serve as a nidus for infection. It was noted, however, that as the amount of oxidized cellulose increased, the incidence of infection increased as well. Thus, despite the antimicrobial properties of oxidized cellulose, it is advisable to use the smallest effective amount if it will be left in the surgical field.

Oxidized cellulose tends to cause relatively little tissue reaction. The gelatinous mass that results from application can be removed without causing rebleeding, and its presence rarely causes foreign body reaction. The rate of absorption depends on where it is implanted, but studies have demonstrated absorption time in the range of 3 to 6 weeks when implanted on cat cortex. Studies have also shown that oxidized cellulose reduces adhesion formation and thus may have some utility in preventing the dura from adhering to cortical surfaces.

Oxidized cellulose does have some disadvantages, though. First, it can inhibit bone formation. When placed in subperiosteal rib resections, oxidized cellulose was associated with decreased bone formation. This leads to the speculation that its use should be minimized when bony fusion or healing is desired. Second, in the product insert, it is advised that oxidized cellulose should not be used to wrap vascular anastomoses, as this can lead to narrowing and stiffening of the wrapped vessels. Lastly, due to its tendency to swell after coming in contact with blood,
Implantation of oxidized cellulose can lead to compressive syndromes. There have been various case reports over time of compressive neuropathies, paresthesias, and even blindness due to compression from swollen oxidized cellulose.32,33

**Microfibrillar Collagen (Avitene)**

Microfibrillar, or microcrystalline, collagen (Avitene, Davol, Warwick, RI), a water-insoluble, partial hydrochloric acid amino salt of collagen in the form of fibers containing microcrystals, was first reported in 1967.34 The first report of its use as a hemostatic agent was in 1969.35 Avitene contains 1-µm microcrystals of purified bovine dermal collagen. Avitene’s proposed mechanism of action is by facilitating aggregation of platelets. Microcrystalline collagen provides a surface for platelets to aggregate to while coagulation factors are released. The interstices of the collagen prevent subsequent loss of platelets.36 Because of this platelet-dependent clotting activity, the effectiveness of microfibrillar collagen is severely decreased in cases of extreme thrombocytopenia (< 10,000/mL).37

Available in either flour or sheet forms, it should be kept dry before use, as moisture decreases its activity. It is also very hydrophilic, and thus will adhere to surgical gloves. Consequently, it is best handled with sterile forceps.25 As with other hemostatic adjuncts, it is a foreign body, and can serve as a nidus for infection. As a result, the smallest effective amount should be used.27 Microfibrillar collagen tends to float off of briskly bleeding surfaces, such as sinus bleeding.38 When used for those applications, it is recommended that a dry sponge be placed over the bleeding surface after application of microfibrillar collagen. The sponge should be left in place for at least 30 seconds, whereupon it may be removed without causing rebleeding. The excess microfibrillar may then be removed by gentle suction or curettage without risk of causing rebleeding.39

The flour form of microfibrillar collagen can be difficult to handle. To facilitate its use, wafers can be made by filling a syringe with the microfibrillar collagen. The tip is then cut off, whereupon the microfibrillar collagen is extruded, yielding a small disk. Another method that has been used is to place the microfibrillar collagen on a bed of oxidized cellulose. The oxidized cellulose is then folded over the microfibrillar collagen, thus forming a “sandwich.” The resultant sandwich may then be placed in areas that would otherwise be difficult to access.40

Given the small particles of the flour form of microfibrillar collagen, it is particularly useful in stopping cancellous bone bleeding. It has demonstrated superior efficacy when compared with other hemostatic agents, such as thrombin alone or thrombin combined with Gelfoam.41,42 In contrast to oxidized cellulose or bone wax, it does not interfere with bone healing; thus, it is useful particularly when fusion is desired.41,43 When used for bleeding bone, it is recommended that the product be firmly packed into the bone surface followed by application of pressure for 5 to 10 minutes.44

Because microfibrillar collagen is composed of foreign proteins, there is a potential for allergic reactions in individuals. Still, collagen is relatively less antigenic, and generally causes only minor inflammatory reactions.45 Depending on where it is implanted, it is usually assimilated by 7 weeks, leaving little residual material.25 It has been associated with adhesions when implanted intraperitoneally in animals,46 but does not tend to cause narrowing of vascular anastomoses, in contrast to oxidized cellulose.31
Thrombin

Thrombin, in its current relatively pure formation, has been in use since the 1930s. It is produced by converting bovine prothrombin to thrombin by thromboplastin in the presence of calcium chloride. It is then processed into powder form and supplied in vials ranging from 1,000 to 10,000 NIH units (1 NIH unit is the amount of thrombin required to clot 1 mL of oxalated plasma). Thrombin is also available as a recombinant formulation (Recothrombin®, The Medicines Company, Parsippany, NJ). Because its action is dependent on fibrinogen, thrombin can cause coagulation in whole blood, plasma, or simply a solution of fibrinogen.

Thrombin can be applied in its powder form directly to bleeding surfaces or can be diluted in sterile saline and applied either as a wash or by spraying. Its most popular use is in combination with a gelatin sponge, where it can be applied directly to bleeding surfaces, synergizing the chemical hemostatic properties of thrombin with the mechanical ones of the gelatin sponge. As mentioned earlier, thrombin should not be used with oxidized cellulose. In addition, it should not be used with microfibrillar collagen, as moistening the microfibrillar collagen destroys its hemostatic properties.

Although thrombin causes very fast clot formation, it is easily washed off. Thus, it is best used in cases of mild to moderate bleeding; it is not sufficient on its own to stop brisk, arterial bleeding. In addition, in cases of severe fibrinogen depletion, thrombin is ineffective. Given that it is bovine in origin, it can be antigenic in humans; thus, allergic reactions can occur. It should also not be allowed to enter the vascular system, as disseminated intravascular coagulation may occur. In animal studies, thrombin caused increased cerebral edema when used in concentrations similar to human neurosurgical procedures (100–1,000 units/cm³). Consequently, it was concluded that the use of thrombin should be minimized to those situations in which other hemostatic methods such as bipolar cautery are insufficient to stop bleeding.

Bone Wax

Bone wax has been in use since the 1800s. Sir Victor Horsley, in 1892, was the first surgeon to use it in a neurosurgery application. With his seminal written contribution to the then-nascent field of neurosurgery, the application of bees’ wax to stop bone bleeding became popularly known as “Horsley’s wax.” The formulation currently in use, known as beeswax, softened with 12% isopropyl palmitate with or without up to 30% paraffin wax, is remarkably similar to the wax that was formulated by Horsley. Because of its ease of use and effectiveness, it remains a popular method of achieving bone hemostasis.

The hemostatic properties of bone wax are purely mechanical. It functions by tamponading bleeding cancellous channels. Because it is insoluble, it is not metabolized or absorbed by the body, thus remaining indefinitely at the site of application. Despite its widespread use, it is not without drawbacks. It can potentially cause chronic inflammation and foreign body granuloma formation, lower the bacterial clearance from cancellous bone, and serve as a nidus for infection. In addition, it can exert local mass effect, and can compress adjacent neural or vascular structures, leading to pain, weakness, blindness, or occlusion of dural sinuses. For this reason, judicious use of bone wax is recommended.
One of the most serious drawbacks is the tendency of bone wax to interfere with bone healing.\textsuperscript{57} It has been observed to interfere with bone healing in sternotomy operations.\textsuperscript{58} In addition, because it is physiologically inert, it may serve as a barrier to bone healing for an indefinite period of time. Because of this, the use of bone wax should be avoided in cases where bone fusion is desired, as in the case of spinal fusions.

Given the drawbacks of beeswax-based bone wax, alternative formulations have been developed. Ostene (Ceremed, Los Angeles, CA), which is composed of watersoluble alkylene oxide block copolymers, has been demonstrated in rat models to be quickly absorbed as well as not to interfere with bone healing. This product is commercially available, but given a relatively short track record, it is not possible to comment on any potential long-term disadvantages.\textsuperscript{51}

### Fibrin Glue

Fibrin glue (Tisseel, Baxter, Deerfield, IL; Evicel, Ethicon, New Brunswick, NJ) is composed primarily of two components: human fibrinogen and human thrombin.\textsuperscript{59} The fibrinogen component is delivered as a “sealer protein,” which is composed of fibrinogen with aprotinin to prevent fibrinolysis. When the two components are combined, it mimics the final stage of the human coagulation cascade.\textsuperscript{60} Upon mixing, the soluble fibrinogen is converted by thrombin into fibrin, thus resulting in a rubbery mass that adheres to tissues, thereby achieving hemostasis. In addition, it also has some sealing characteristics; thus, it has found widespread usage as an adjunct to prevent cerebrospinal fluid (CSF) leakage.\textsuperscript{61}

The only on-label indications for fibrin glue are hemostasis in the setting of cardiopulmonary bypass and splenic injuries, and as a sealant to prevent leakage from colonic anastomoses following reversal of temporary colostomies. It is explicitly stated in the product insert that fibrin glue has not been evaluated for safety in neurosurgical procedures. Still, despite these statements, fibrin glue has become a popular hemostatic adjunct and sealant in neurosurgical procedures. Also, because fibrin glue does not rely on host factors for hemostasis, it can effectively be used even in heparinized patients.\textsuperscript{62} Despite its off-label usage, it is widely reported as a hemostatic agent in neurosurgical procedures, including stopping epidural, cortical, and dural sinus bleeding. It has also been used in peripheral nerve repairs, and has been found to be comparable to suture repair in various animal studies.\textsuperscript{63}

Fibrin glue can be delivered either by dual-barrel syringe or spray. In either case, after the fibrin glue has been applied, it should be fixed or held in place for 3 to 5 minutes to ensure adherence to tissues. If applied by spray, care should be taken not to hold the device too close to the tissue, as there have been cases of air embolisms.\textsuperscript{64} In addition, only a thin layer should be applied. Excess clot thickness can delay the natural wound healing process. Oxidized cellulose may cause denaturation of the proteins in fibrin glue, decreasing its efficacy.\textsuperscript{61} Because fibrin glue is derived from human pooled plasma, there exists a theoretical risk of disease transmission. In addition, it also contains synthetic aprotinin, for which cases of anaphylaxis have been reported.\textsuperscript{65,66}
Cautery

Monopolar Cautery

Monopolar (or unipolar) cautery was developed in 1920s by William T. Bovie, a physicist at the Massachusetts Institute of Technology. In cautery's earliest incarnation, Bovie found that excellent coagulation could be produced by a spark-gap generator producing irregular damped waveforms. This generator was also able to produce a synchronous sinusoidal waveform, thus resulting in cutting. First brought into the surgical arena by Harvey Cushing, cautery revolutionized the field of surgery, and brain surgery in particular. It enabled Cushing to perform tumor removal in areas that had been previously inaccessible due to uncontrollable bleeding. Over the years, modifications have been made to the original monopolar cautery unit, but the mechanism of action remains the same.

The cutting or coagulation action of the monopolar unit is delivered by the active electrode, which provides a high current per cubic millimeter due to its small size. Accordingly, the return path is provided a much larger ground plate. The coagulating waveform is arrhythmic and random, thus eliminating molecular resonance. This lack of resonance with tissue results in coagulation rather than cutting. The current then travels through the tissues to the ground plate, preferentially traveling through higher conductivity structures such as blood vessels and nerves. This results in two effects. First, there is significant current and heat generation 1 to 2 cm away from the electrode, making it unsuitable for microsurgery. In addition, because the current preferentially travels through nerves and blood vessels, more damage may occur to these structures as well as inducing nerve or muscle activation.

If the waveform is sinusoidal and regular, as opposed to arrhythmic, a cutting current will be generated. In the range of 0.5 to 3 MHz, it induces molecular resonance, thus causing division of tissues while minimizing stimulation of muscle and nerve tissues. If the power is decreased to too low a level, coagulation rather than cutting will occur. This is an inherently inferior technique for coagulation, as partial contact will cause cutting due to higher density of current delivery. As with coagulation settings, cutting current causes heat generation 1 to 2 cm distant from the point of contact and will travel preferentially along nerves and blood vessels, causing increased damage along those pathways. In either case, if the electrode is held close to, but not touching, tissue, sparking will occur. This fulguration will result in destruction of tissues.

Bipolar Cautery

Due to the need for fine control of cauterization, bipolar cautery units were developed. The first bipolar cautery system was devised by Greenwood by connecting one side of forceps to the electrical current and the other to the ground plate. The power setting was also accordingly decreased, as the current spread was significantly decreased compared with monopolar cautery. This system was not isolated, however. That is, if only the electric current side of the forceps came in contact in tissues, the current could spread through the patient via any grounding contact on the patient's body. Effectively speaking, this was of minor concern, as the power utilized was much less compared with monopolar cautery, thus limiting the possi-
bility of indiscriminate tissue damage. Despite the effectiveness and utility of this system, it was not popularized and was used only by Greenwood himself.\(^{69}\)

With advances in solid-state electronics, Malis developed the bipolar cautery unit that is still in use today. As opposed to spark generators, which were used previously, solid-state generators were capable of producing finely controlled synchronous or asynchronous waves that could either cut or coagulate as needed with fine control. This system was also isolated; thus, no current would spread if only one side of the forceps came in contact with the patient. As with monopolar cautery, synchronous waves result in molecular resonance, thus leading to cutting. If the wave is asynchronous, no resonance occurs, thus resulting in coagulation.\(^{67}\)

The current passes predominantly between the forceps with very little leakage through the patient. As a result, the power needed as compared with monopolar cautery is much reduced. In addition, because of the relative lack of current spread, bipolar cautery is appropriate for use in microsurgery.\(^{70}\) The closer the tips of the forceps are held together, the more focused the current delivery will be with less current leakage. It is thus advised to hold the tips as close together as possible for maximal utility. Irrigation is generally recommended, as this prevents charring or sticking.\(^{71}\) The modern bipolar unit has an irrigation unit integrated into the bipolar forceps. The forceps are also bayoneted to prevent obstruction of view when used in microsurgery.

Over time, the tips of the bipolar forceps become rough or pitted due to electrolysis. Uneven contact of the tips with tissue can result in sticking of tissues to the forceps. Current bipolar forceps tips are composed of a metallic alloy that is resistant to pitting or roughening due to electrolysis. Accordingly, it is recommended that the tips never be cleaned with an abrasive “scratch” pad. Instead, a clean wet sponge is as effective and will avoid damaging the forceps.\(^{67}\)

**Laser**

Laser, an acronym for *light amplification by stimulated emission of radiation*, has attained some utility in the neurosurgical armamentarium. First used in the 1960s, lasers became increasingly popular in the 1980s. However, due to their perceived inefficiency, lack of accuracy (compared with bipolar cautery), and nonergonomic characteristics, its use fell out of favor. Today, although lasers are still being used in the neurosurgical arena, its use is not nearly as widespread as may have been predicted when they were first developed and popularized.\(^{72}\)

Lasers are typically used in three situations in surgery: photocoagulation, photovaporization, and photoactivation. Which of these three actions will take place is dependent on the properties of the laser and the tissue itself. Laser properties include power output, wavelength, beam density, and time of exposure. The properties of tissue include the absorption coefficient, the extinction length, and the presence of light-absorbing chromophores.\(^{73}\) Today, there are three types of laser that are commonly used in neurosurgery. First, the CO\(_2\) laser, with a wavelength of 10.6 µm, can produce coagulation, cutting or vaporization.\(^{74}\) The argon laser, with a shorter wavelength of 488 to 516 nm, is scattered more widely in tissue. As a result, the energy delivered is dispersed more widely as heat causing a broader zone of coagulation.\(^{73}\) Lastly, the neodymium: yttrium-aluminum-garnet (Nd:YAG) laser (wavelength 1060–1340 nm) spreads even more widely through tissues, causing slow, deep heating of tissues. This results in a wide area of coagulation.\(^{75}\) The Nd:YAG
laser was also investigated in vascular anastomoses in the 1980s, though its relatively inexact heating effects limited its utility near eloquent tissues.\textsuperscript{76}

The first lasers delivered high-energy pulses. When used in the first animal experiments, they were found to cause rapid heating and expansion of mouse brains, causing instantaneous death due to herniation.\textsuperscript{77,78} When the power was lowered, continuously powered lasers were developed, which enable slower, more finely controlled heating to be delivered to tissues, resulting in coagulation or cutting with finer accuracy. It was these experiments that described the characteristic effects of laser vaporization, a vaporized core surrounded by a rim of desiccated tissue. This, in turn, was surrounded by a zone of edematous tissue caused by heat.\textsuperscript{79,80}

Following these experiments, lasers were then used in tumor extirpation. The concept of surgery without requiring actual contact with tissues was quite attractive. It was demonstrated to be effective in a variety of situations including glomas, fibrous tumors such as meningiomas and peripheral nerve tumors, and scar tissue as in the case of tethered cords.\textsuperscript{72} Lasers were also investigated in endoscopic techniques, but were found to have limited utility due to loss of energy when refracted through the fiberoptic cables available at the time.\textsuperscript{72} Although certainly efficacious, lasers were often found to be slower than other available technologies, including bipolar cautery and ultrasonic aspiration. In addition, due to the relatively large size and cumbersome ergonomics of the equipment, laser use fell out of favor.\textsuperscript{81}

Recently, a newer CO\textsubscript{2} laser has been developed by OmniGuide (Cambridge, MA). It consists of a flexible, hollow fiber lined with an omnidirectional mirror, ameliorating some of the disadvantages of previous CO\textsubscript{2} lasers. Because of its low profile, it can be used in microsurgical situations.\textsuperscript{82} It remains to be seen if lasers will gain widespread usage in neurosurgery.

\textbf{KEY POINTS}

- Hemostatic agents are categorized as chemical, mechanical, or thermal.
- All hemostatic agents are foreign bodies, and can serve as a nidus for infection. The minimum necessary amount should be used.
- Hemostatic agents are derived from animal proteins, and thus can be antigenic.
- Hypersensitivity reactions have been seen with thrombin and fibrin glue.
- Gelatin sponge and oxidized cellulose swell and can cause compression of adjacent structures.
- Bone wax and oxidized cellulose can retard bone formation, limiting its use where bone healing is desired.
- Bipolar cautery delivers finely applied current and is suitable for microsurgery, in contrast to monopolar cautery.
- Lasers, although effective, have not found widespread use in neurosurgery.
**REVIEW QUESTIONS**

1. Collagen sponge falls into which one of the following categories of hemostatic agents?
   A. Caustic
   B. Mechanical
   C. Styptic
   D. Thermal
   E. None of the above

2. Which components of blood are necessary for the function of thrombin?
   A. Factor VII
   B. Fibrinogen
   C. Platelets
   D. Tissue factor

3. Pooled blood products, with inherent risk of communicable disease, are used to develop which of the following hemostatic agents?
   A. Fibrin glue
   B. Gelatin sponge
   C. Microfibrillar collagen
   D. Oxidized cellulose (Surgicel)

4. Classic bone wax dissolves over which time frame?
   A. 1 to 3 weeks
   B. 2 months
   C. 1 year
   D. Never

5. True or false: Bipolar cauter poses requires more power than monopolar cauter.

6. Which of the following hemostatic agents does not swell?
   A. Bone wax
   B. Gelatin sponge
   C. Microfibrillar collagen
   D. Oxidized cellulose
   E. False

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VI
Management of Bleeding, Coagulation, and Venous Thrombosis in Specific Neurosurgical Conditions
Patients with primary or metastatic brain tumors are predisposed to venous thromboembolism (VTE) due to an underlying hypercoagulable state, particularly in the postoperative period.\textsuperscript{1,2} The etiology of thrombosis is likely multifactorial and includes tissue factor–induced activation of coagulation, vessel wall injury from chemotherapy or radiation, and stasis as a result of surgery or neurologic deficits.\textsuperscript{3,4} Antithrombotic prophylaxis has been routinely used in patients undergoing general and orthopedic surgery and in hospitalized medical patients, but its adoption has been slower in ambulatory patients with brain tumors because of the concern about anticoagulant-associated intracranial bleeding. The risk of developing clots due to a hypercoagulable state and neurosurgical procedures needs to be balanced between the risk of precipitating a hemorrhage into the tumors of these patients. This chapter discusses the risk of anticoagulation and antiplatelet therapy in patients with brain tumors.

**Risk of Venous Thromboembolism**

Although the actual incidence of venous thromboembolism in patients with primary or metastatic brain tumors is unknown, early studies have suggested an incidence of 25% or higher.\textsuperscript{5} More recently a lower rate has been observed in a larger retrospective analysis of 9,489 patients with malignant gliomas, in which 7.5% of patients had a VTE event.\textsuperscript{2} Another study reported an incidence of 18% in a prospective study of patients with malignant gliomas.\textsuperscript{6} Similarly, in the most recent randomized study comparing dalteparin to placebo (PRODIGE), authors report an incidence of 17% in patients with malignant gliomas.\textsuperscript{7} Interestingly, the risk of VTE in pediatric patients with brain tumors is exceedingly low. In a study of 462 children with brain tumors, the incidence of clinical VTE was only 0.64%.\textsuperscript{8}

**Risk of Bleeding from Tumor**

The risk of intracranial bleeding into a brain tumor, causing neurologic deterioration, raises serious concerns about using anticoagulant or antiplatelet agents in patients with known brain tumors. The risk of anticoagulant-associated intracranial bleeding within a brain tumor is difficult to assess because the rate of spontaneous tumor hemorrhage is significantly different among tumor types. Metastatic brain lesions from choriocarcinoma, melanoma, renal cell carcinoma, and thyroid cancer have a particularly high rate of spontaneous hemorrhage, whereas lung, breast, and prostate cancer have a much lower rate.\textsuperscript{9} The risk of intracranial bleeding in cancer
patients with systemic disease and occult metastases raises concerns whether such patients should undergo brain imaging prior to the use of anticoagulants or antiplatelet agents. However, there are very few data to support such practice. In regard to gliomas, one study suggests that the use of anticoagulants is associated with 2 to 4% symptomatic bleeding.10

**Prevention of Venous Thromboembolism in Patients with Brain Tumors**

Primary prophylaxis with anticoagulants has generally not been recommended in patients with brain tumors except in the perioperative period, where the frequency of VTE is highest, likely due to immobilization and tissue-factor release from damaged blood vessels.2,11 One of the first studies looking at VTE prophylaxis in patients with brain tumors was performed at the University of Michigan. The researchers observed a low incidence of deep vein thrombosis (DVT) (1.4%) and pulmonary embolism (PE) (1.0%) in neurosurgical patients undergoing surgery while using only sequential compression devices (SCDs). However, analysis of their cohort by diagnostic category showed that 56% of their VTE complications occurred in patients with brain tumors.12 The apparent ineffectiveness of SCD prophylaxis for patients with intracranial neoplasms led the researchers to initiate a prospective study comparing the effects of preoperative administration of the low molecular weight heparin (LMWH) enoxaparin with that of SCDs alone; 68 patients completed the study, and the researchers found no statistical difference in their primary end point, which was postoperative DVT. Postoperative intracranial hemorrhage (ICH) did not occur in the patients with only SCDs, whereas five of 46 patients receiving LMWH (prophylactic dosing—30 mg twice daily) suffered a clinically significant ICH, which led to termination of the study. The researchers’ conclusions were that initiation of enoxaparin at the time of anesthesia induction increases the risk of postoperative intracranial hemorrhage.

In contrast, there is class I and II evidence supporting the use of chemical prophylaxis in patients with central nervous system (CNS) malignancies undergoing surgery. The first comes from Tel Aviv University in Israel and was a prospective, randomized, double-blinded study that looked at the safety of perioperative minidose heparin in patients undergoing brain tumor surgery.13 Fifty-five patients were treated with 5,000 units of heparin compared with 48 patients receiving placebo starting 2 hours before surgery; treatment was continued until full mobilization or 7 days, whichever came first. The authors found no statistical difference in bleeding tendencies during the intra- or postoperative periods between the two groups. They concluded that perioperative minidose heparin was safe in patients undergoing craniotomy for CNS tumors and recommended routine use of heparin in these patients for the prevention of VTE. This study is likely the most cited in regard to evidence-based medicine and the use of perioperative anticoagulants to prevent VTE complications in patients harboring CNS malignancies.

Venous thromboembolic complications following meningioma resection is well documented in the literature and led neurosurgeons at the University of California, San Francisco (UCSF) to look at the use and safety of postoperative enoxaparin in these patients.14 In a retrospective case-control study of 86 patients with intracranial meningiomas who underwent craniotomy, the authors identified 24 patients who started receiving enoxaparin within 48 hours after surgery and compared this treatment with a group of 62 patients who received no pharmacological prophy-
Risk of Anticoagulants and Antiplatelet Agents

The authors found that enoxaparin did not increase the incidence of ICH following surgical resection, and the incidence of VTE complications was 0% in the LMWH group compared with 4.8% in the non-enoxaparin group, which was not statistically significant. The authors concluded that there was no significant increase in postoperative hemorrhage in patients who received LMWH postoperatively compared with those who did not. This study is somewhat limited by its retrospective nature and small numbers.

Long-Term Venous Thromboembolism Prophylaxis in Brain Tumor Patients

The previous studies focused on VTE prevention during the perioperative period and did not address long-term VTE prophylaxis. Extended use of the LMWH dalteparin as primary prophylaxis in patients with newly diagnosed malignant gliomas was recently assessed in the PRODIGE trial. This study was a blinded, randomized, placebo-controlled trial that enrolled 186 patients to receive either dalteparin or placebo (within 4 weeks of diagnosis/surgery) for 6 months, with an option to continue the study medication for up to 12 months. The incidence of clinically evident VTE at 6 months was lower among those receiving dalteparin (11 versus 17% with placebo), but was not statistically significant. Additionally, ICHs were more common in patients treated with LMWH compared with placebo (5% versus 1%), which also was not statistically significant. This trial confirmed the substantial risk of VTE complications in patients with malignant gliomas. Although there were trends toward reduction of VTE and increased ICH, the trial did not have sufficient statistical power to enable drawing definitive conclusions about the risk/benefit of long-term anticoagulation in these patients. Similar to these findings, in a phase 1 safety trial involving 40 patients with malignant gliomas, clinicians at Duke University reported that one patient developed a DVT and another developed ICH following daily tinzaparin administration (another LMWH) for a median 5 months. A larger phase 2/3 study is on the way.

More studies look at the general question of VTE prophylaxis in neurosurgical patients compared with neurosurgical patients harboring a brain tumor. Management for brain tumor patients must be put into this context. In general, it is assumed that the incidence of VTE is higher among patients undergoing surgery for a brain tumor compared with other neurosurgical procedures; nonetheless, safety and efficacy of anticoagulation can still be assessed and extrapolated from neurosurgical patients who do not have brain tumors. Eight randomized clinical trials (RCTs) have been published that evaluate either heparin or LMWH in patients undergoing elective cranial neurosurgery; two studies have already been discussed, and three meta-analyses reviewing this subject have been published. The most recent review and meta-analysis by Hamilton and coworkers is the most comprehensive and analyzes these eight RCTs. Six of the RCTs evaluated either heparin or LMWH versus a control (placebo) group and included 1,170 patients. Five of the six trials found a significant reduction in the risk of VTE complications (symptomatic or asymptomatic) with perioperative heparin/LMWH prophylaxis. The pooled risk ratio for VTE with heparin use was 0.58 from the six RCTs. ICH was more common in those receiving anticoagulation prophylaxis, but five of the six RCTs found no statistical increase in ICH in patients receiving perioperative anticoagulation. The one study showing a significant increase in ICH among anticoagulated patients, from Dickinson and coworkers at the University of Michigan, was
previously discussed. Hamilton and coworkers’ meta-analysis predicts that for every 1,000 patients who receive heparin prophylaxis, 91 VTE events will be prevented, but seven patients will have a major ICH. They conclude that for patients undergoing elective cranial neurosurgery, heparin reduces the risk of VTE but may also increase the bleeding risk, and the balance only slightly favors heparin prophylaxis.

**Bevacizumab**

Bevacizumab, a monoclonal antibody that binds to vascular endothelial growth factor, is Food and Drug Administration (FDA) approved for the management of recurrent glioblastoma and has been used experimentally in the treatment of other brain tumors. It presents special considerations with regard to prophylaxis for VTE, as it is associated with both an increased risk of bleeding into a primary brain tumor and with VTE. The risk of ICH has limited its use in patients requiring anticoagulation for venous thrombosis. Two studies have looked at the safety of concurrent administration of bevacizumab and anticoagulation. The first was a small retrospective analysis of 21 patients who received therapeutic-dose anticoagulation (LMWH or warfarin—not perioperative) and bevacizumab. No serious ICH occurred, and only three small, nonsymptomatic hemorrhages were identified, compared with seven patients who had symptomatic ICH who were not anticoagulated. In contrast, a recent observational study of 64 patients receiving concurrent bevacizumab and anticoagulation found seven patients with ICH (11%) compared with 218 patients not receiving anticoagulation, where only two patients had serious ICH (1%). Because bevacizumab use is increasing, larger studies will be necessary to determine if concurrent anticoagulation is safe.

**Recommendations for Venous Thromboembolism Prophylaxis in Patients with Brain Tumors**

After reviewing the available data on VTE prophylaxis, there is no universal agreement that patients should receive anticoagulation or for how long. The two studies most applicable for patients with brain tumors provide contradictory results. Dickinson and coworkers found a statistical increase in ICH when LMWH (prophylactic dosing) was initiated prior to surgery. However, Constantini et al’s study did not find an increase in ICH when low-dose heparin was initiated before surgery. Does this difference reflect a difference in the two drugs, a difference in methodology, or a difference in patient selection? The answer remains unclear. The largest body of evidence on this topic is provided by the recent meta-analysis. Its conclusions are probably most accurate, and suggest that pharmacological prophylaxis does reduce the risk of VTE but also with a trend toward increased bleeding risk with a balance only slightly favoring anticoagulation.

Accordingly, at our institution we recommend that prophylactic anticoagulation be initiated only during the perioperative period in patients with brain tumors, as there is not yet statistically significant evidence to support long-term use in ambulatory patients. It is our practice to initiate heparin prophylaxis (5,000 mg twice daily) the day after surgery, as long as postoperative imaging is negative for bleeding or other complications that may necessitate return to the operating room, and anticoagulation is continued until discharge.
Treatment of Venous Thromboembolism in Patients with Brain Tumors

Patients with brain tumors and a DVT or PE have been historically treated with inferior vena cava (IVC) filters rather than anticoagulation due to the concern over an increased risk of anticoagulant-associated intracranial bleeding. However, anticoagulation is now the first-line therapy because the incidence of IVC filter complications is higher than originally thought, and the risk of hemorrhage secondary to anticoagulation is not as high as expected. In one study of 42 such patients, 57% developed IVC filter thrombosis, recurrent DVT, or postthrombotic syndrome.

Warfarin Anticoagulation for Venous Thromboembolism in Patients with Brain Tumors

Several retrospective case-control studies have suggested that, outside the perioperative period, anticoagulation with warfarin is safe as long as the levels are carefully controlled. In one report, two of 103 patients (1.9%) of patients with a malignant glioma receiving warfarin for VTE developed a symptomatic intratumoral hemorrhage, compared with 2.2% of 272 malignant glioma patients without VTE or anticoagulation. In a series of 51 patients with metastatic brain tumors, three (6%) developed ICH. However, two of the patients had supratherapeutic warfarin levels. Although randomized comparisons are not available, data from these case studies suggest that warfarin is reasonably safe to use in patients with VTE and brain tumors.

Low Molecular Weight Heparin for Venous Thromboembolism in Patients with Brain Tumors

No studies directly report the use of full-therapeutic dosing of LMWH for treatment of VTE in patients with brain tumors or neurosurgical patients. Several studies already mentioned looked at LMWH for VTE prophylaxis in neurosurgical patients; it appears to be relatively safe according to the recent meta-analysis by Hamilton and coworkers. Additionally, there are no randomized studies comparing warfarin and LMWH anticoagulation specifically in patients with brain tumors. In the large randomized CLOT study comparing warfarin and LMWH in 673 patients with systemic cancer and VTE, LMWH was found to be more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding. However, only 34 patients had primary brain tumors in this study.

Recommendations for Venous Thromboembolism Treatment in Patients with Brain Tumors

To summarize, the management of venous thromboembolism in patients with brain tumors requires a balance between the effectiveness of treatment and the risk of ICH or other side effects. All experts agree that VTE complications need to be treated, and treatments include oral anticoagulation with warfarin, LMWH, or
placement of an IVC filter. Based on the available data, which is mostly class III evidence and expert opinion, we suggest that LMWH rather than warfarin be used to treat VTE in patients with brain tumors because data from the CLOT trial found increased effectiveness in preventing recurrent thromboembolism, combined with the lower likelihood of developing supratherapeutic levels with weight-based LMWH administration. Patients harboring untreated metastatic brain tumors that have an increased risk of hemorrhage (melanoma, choriocarcinoma, renal cell carcinoma, and thyroid cancer) should have an IVC filter be placed until the tumors have been treated.

Antiplatelet Therapy in Brain Tumor Patients

Antiplatelet agents are the cornerstone for primary and secondary prevention of coronary artery disease (CAD) and cerebrovascular disease, and are especially important after percutaneous coronary interventions (PCIs). Over 2 million PCI procedures are performed annually in industrial nations, and this number continues to grow yearly, with over 90% of all procedures involving stent placement.\(^{32}\) As the prevalence of CAD continues to increase, so will antiplatelet use. Recent reports suggest that up to 5% of patients who undergo cardiac stent placement will also undergo some type of surgery within the first year after coronary stenting.\(^{32}\) This subset of patients presents surgeons, anesthetists, and cardiologists with the problem of deciding between the risk and benefits of continued antiplatelet therapy, meaning the risk of major operative bleeding versus possible coronary stent thrombosis. Because of the fear of intraoperative bleeding, it is generally accepted to stop antiplatelet therapy 5 to 10 days before surgical procedures. Unfortunately, studies that look at perioperative hemorrhage risk with antiplatelet therapy have been performed mainly in the orthopedic and cardiac surgery patients and are not generally applicable to neurosurgical patients.

No randomized controlled trials have compared the risk of bleeding in neurosurgical patients undergoing craniotomy who receive antiplatelet therapy with those who do not. Furthermore, no studies have investigated the risk of hemorrhage in patients with brain tumors who are taking antiplatelet agents. One study from the United Kingdom looks at avoidable risk factors that were associated with postoperative hematoma in neurosurgical patients. Over the 5-year period of study, 6,668 neurosurgical procedures were performed and 71 postoperative hematomas required surgical evacuation.\(^{33}\) Interestingly, the most frequent diagnosis leading to postoperative hematoma was meningioma. Risk factors for postoperative bleeding included low platelet count, prolonged prothrombin time, anticoagulant use that was not reversed, and heavy alcohol use; however, the most commonly associated risk factor was administration of aspirin, dipyridamole, or nonsteroidal anti-inflammatory drugs during the 2 weeks preceding the surgical procedure.\(^{33}\) A large meta-analysis examined the impact of low-dose aspirin in patients undergoing any surgery and found that patients on aspirin have an increase in perioperative bleeding complications of 50%; however, this did not translate into an increase in morbidity or mortality except for neurosurgical patients (referring to the previous study in the United Kingdom).\(^{34}\)

Members of the Neuroanaesthesia Society of the United Kingdom were asked in 1997 about their policy regarding discontinuation of low-dose aspirin prior to intracranial surgery.\(^{35}\) Their answers were very inhomogeneous, but the majority
of respondents felt that aspirin was a risk factor for hemorrhagic complications associated with intracranial procedure, but most have no specific policy regarding preoperative discontinuation. In a similar survey among neurosurgeons practicing in Germany, three quarters of the 138 neurosurgeons who responded felt that aspirin was a risk factor for hemorrhagic complications associated with intracranial procedures and more than half reported personal experiences of such problems. They also reported that the majority of neurosurgical facilities in Germany have distinct departmental policies concerning discontinuation of antiplatelet therapy preoperatively, an average of 7.3 days before surgery.

At our institution, we recommend stopping antiplatelet therapy 5 days prior to cranial neurosurgery. However, we recognize there is no evidence for this recommendation, and it is hoped that, in the future, well-designed studies may provide us with better guidance.

**KEY POINTS**

- In patients with primary or metastatic brain tumors, the risk of VTE is increased.
- In patients with brain tumors, prophylactic anticoagulation should be initiated during the perioperative period. Although there were trends toward reduction of VTE and increased intracranial hemorrhage with the use of prophylactic anticoagulation in ambulatory patients, no definitive conclusions can be drawn about the risk/benefits of long-term anticoagulation.
- VTE complications need to be treated, and treatments include oral anticoagulation with warfarin, unfractionated heparin, LMWH, or placement of an IVC filter.
- If there are no strong indications for its use during surgery, stop antiplatelet therapy at least 5 days prior to cranial surgery.

**REVIEW QUESTIONS**

1. The etiology of thrombosis in brain tumor patients is due to all of the following except:
   A. Anticonvulsant use
   B. Neurologic deficits
   C. Surgery
   D. Tissue factor–induced activation of coagulation
   E. Vessel wall injury from chemotherapy or radiation

2. True or false: Anticoagulation is first-line therapy for VTE as compared with IVC filter in patients with primary brain tumors.

3. Risk factors for postoperative bleeding include which of the following?
   A. Anticoagulant use that was not reversed
   B. Low platelet count
   C. Prolonged prothrombin time
   D. Recent aspirin use
   E. All of the above
4. All of the following are comparative advantages of the use of LMWH over warfarin in patients with brain tumors except:
   A. Less supratherapeutic dosing
   B. Less bleeding risk in trials
   C. Increased effectiveness in preventing VTE
   D. Less blood monitoring

5. What is the most appropriate therapy for a patient suffering a postoperative hematoma who has been on aspirin, and has a normal prothrombin time (PT) and partial thromboplastin time (PTT)?
   A. Infuse platelets
   B. Administer factor VII
   C. Infuse fresh frozen plasma
   D. Hemodialysis
   E. Protamine followed by vitamin K

References


ANSWER KEY

1. A
2. True
3. E
4. B
5. A
Risk of Anticoagulants and Antiplatelet Agents in Common Neurovascular Conditions

Benjamin W.Y. Lo and R. Loch Macdonald

There is a paucity of high-level evidence (lack of prospective studies) investigating the risks of anticoagulants and antiplatelet agents in patients with common neurovascular conditions. In view of the current state of evidence, clinical decisions regarding initiating or maintaining a patient on a specific antiplatelet or anticoagulant drug depend on the balance of the following risks:

1. Risk of bleeding with each type of vascular lesion or malformation
2. Risk of intracranial hemorrhage with each type of anticoagulant/antiplatelet agent
3. Additive risk of increased bleeding with vascular malformation and anticoagulant/antiplatelet (from disruption of thrombotic clot)
4. Risk of an event (e.g., cardioembolic stroke from atrial fibrillation) for which an anticoagulant/antiplatelet agent is initiated
5. Risk reduction of an event after initiation of an agent

Only level 3 evidence (evidence from case series, historical controls, case reports, and expert opinion) is available regarding risk management, leading to high degrees of clinical uncertainty.

Coagulation Cascade and Acquired Defects

The initial response to vessel injury begins with formation of the platelet plug, which depends on normal vascular and platelet function. Defects in one or a combination of these components are reflected in a prolonged bleeding time. Bleeding disorders may be secondary to defects in the activity of platelets, blood vessel endothelium, or one or more coagulation factors (coagulopathy). The causes may be congenital or acquired.

This chapter focuses on acquired causes of defects in platelet activity, such as medications, renal diseases, myelodysplasia, and myeloproliferative disorders, and on acquired defects in coagulation, such as exposure to anticoagulants, vitamin K deficiency, liver disease, disseminated intravascular coagulopathy (DIC), trauma, and acquired factor inhibitors.

The classic representation of the coagulation cascade includes an extrinsic pathway initiated by tissue injury and a contact (intrinsic) pathway, leading to the common pathway (Fig. 19.1). This system is useful for understanding causes of prolonged activated partial thromboplastin time, which include heparin, lupus anticoagulant, deficiencies of factors VIII, IX, and XI, and von Willebrand disease. Elevated prothrombin time may be due to warfarin, vitamin K deficiency, liver dys-
Bleeding, Coagulation, and Venous Thrombosis

Thrombin time depends on the final step of the coagulation cascade (conversion of fibrinogen to fibrin). Therefore, this test is sensitive to detection of fibrinogen abnormalities and inhibitors acting at this level (for example, heparin).

Current understanding of coagulation, however, is that in vivo it is a three-step process centered on cell surfaces (Fig. 19.2). Multiple mechanisms exist to localize coagulation to the site of injury. Factors VII and VIIa have little enzymatic activity unless tissue factor is present and there is very little circulating tissue factor. Amplification requires binding of platelets to the site. Inhibitors of coagulation, such as antithrombin 3, inactivate any circulating factor Xa and thrombin (factor II). Thrombin also binds thrombomodulin on adjacent undamaged vessels, which activates protein C and, in a cascade, protein S, which in turn inactivate factors Va and Vlla. Circulating tissue factor pathway inhibitor also inhibits the tissue factor—factor VIIa complex.

Fibrin clot must be maintained for long enough to permit repair of vascular injury, or delayed bleeding may occur. Fibrinolysis, however, is initiated under various circumstances by activation of plasminogens (tissue and urokinase types) to plasmin, which degrades fibrin to fibrin degradation products (Fig. 19.3). Fibrinolysis can be detected by measurement of fibrin degradation products and D-dimer. D-dimer is a nonspecific product of plasmin degradation of fibrin. Normal inhibitors of the conversion of plasminogen to plasmin are plasminogen activator inhibitor (PAI-1), and thrombin-activatable fibrinolysis inhibitor (TAFI, mainly α2-antiplasmin). Currently available inhibitors of fibrinolysis include tranexamic acid and amino-caproic acid.

![Fig. 19.1 Classic view of coagulation cascade showing extrinsic and intrinsic pathways. aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; PT, prothrombin time.](image-url)
Fig. 19.2  Drawing of the three phases of cell-based coagulation.\textsuperscript{1} Coagulation begins primarily by initiation with tissue factor (TF), which is present on the subendothelium, tissues not normally exposed to blood, activated monocytes, and endothelium when activated by inflammation.\textsuperscript{2} Factors VII and VIIa bind to tissue factor and adjacent collagen. The factor VIIa tissue factor complex activates factor X and IX. Factor Xa activates factor V, forming a prothrombinase complex (factor Xa, Va, and calcium) on the tissue factor expressing cell. Coagulation is amplified as platelets (Pl) adhere to the site of injury in the blood vessel. Thrombin is activated by platelet adherence and acts then to fully activate platelets, enhance their adhesion, and release factor V from the platelet \(\alpha\) granules. Thrombin on the surface of activated platelets activates factors V, VIII, and XI, with subsequent activation of factor IX. The tenase complex (factors IXa, VIIIa, and calcium) are now present on platelets where factor Xa can be produced and generate another prothrombinase complex on the platelet so that there can be large-scale production of thrombin. Propagation is the third stage and is a combination of activation of the prothrombinase complexes that allow large amounts of thrombin to be generated from prothrombin. More platelets can be recruited, as well as activation of fibrin polymers and factor XIII.
Unruptured Intracranial Aneurysms

Incidental intracranial aneurysms are present in 2% of adults. Several studies have estimated the risk of rupture of unruptured intracranial aneurysms. These may be found in patients who have multiple intracranial aneurysms presenting with subarachnoid hemorrhage (SAH) from one of the aneurysms, when an aneurysm becomes symptomatic but not ruptured, or incidentally. Wermer and colleagues reported a meta-analysis of 19 studies including 4,705 patients with 6,556 unruptured intracranial aneurysms followed for 26,122 patient-years. The risk of rupture was 1.2% per patient year in the first 5 years of follow-up, 0.6% per year between 5 and 10 years, and 1.3% beyond 10 years. The risk of rupture was significantly higher in patients over 60 years of age, females, Japanese or Finnish patients, those with larger aneurysms or posterior circulation aneurysms, or if the aneurysm was symptomatic but unruptured. Smoking was associated with increased risk of rupture but was not significant. Growth of aneurysms is believed to be a risk factor for rupture, but may not be detected in natural history studies because these patients are treated and removed from analysis. The largest study of unruptured aneurysms included 1,692 patients with 2,686 aneurysms followed for a mean of 4.1 years. Cumulative 5-year risk of rupture was lower than the numbers above and was increased in patients with a prior SAH, an aneurysm of larger size, and an aneurysm located in the posterior circulation. In Japan, Ishibashi et al followed 419 patients with 529 unruptured aneurysms for a mean of 2.5 years. Nineteen aneurysms ruptured, for a 1.4% rupture rate per year. Risk factors for rupture were
increasing size, a history of SAHs, and posterior circulation aneurysm (Table 19.1). Other risk factors for rupture that are less well documented include various morphological characteristics of the aneurysm (daughter loculi, irregular shape, high aspect ratio), growth of the aneurysm on serial imaging, preexisting hypertension, and family history of intracranial aneurysms.8

The risk of morbidity and mortality from aneurysm rupture also is important to consider. Mortality in studies of unruptured aneurysms that then rupture ranged from 42 to 65%.5,6,9 Furthermore, at least 50% of survivors have permanent cognitive and neurologic impairment.10

Antiplatelet Drugs and Aneurysms

Patients with unruptured aneurysms frequently harbor risk factors for ischemic heart and cerebrovascular disease and are candidates for treatment with antiplatelet drugs. The beneficial effects of antiplatelet drugs, particularly acetylsalicylic acid, have been reviewed. There is class 1, level A evidence to support the use of antiplatelet drugs (acetylsalicylic acid, acetylsalicylic acid plus dipyridamole, or clopidogrel) for secondary prevention of recurrent stroke and cardiovascular events in patients with noncardioembolic ischemic stroke or transient ischemic attack,11 including those with atrial fibrillation who cannot take anticoagulants.12 The relative risk reduction for any type of stroke (ischemic or hemorrhagic) is 15%, and that for overall vascular death and disease is 20%.13 Compared with placebo, acetylsalicylic acid (aspirin) decreased vascular events (and their morbidity and mortality) in patients with coronary, cerebrovascular or peripheral vascular disease (odds ratio [OR] = 0.71, 95% confidence interval [CI], 0.67–0.76; OR = 0.87, 95% CI, 0.82–0.93; and OR = 0.50, 95% CI, 0.29–0.88, respectively).13,14 The risk of major hemorrhage, on the other hand, was almost doubled by aspirin (OR = 1.87, 95% CI, 1.51–2.32 for all three indications).14 These numbers grossly translate, depending on the indication and events prevented, to roughly 20 to 40 vascular events and deaths prevented when 1,000 patients are treated with antiplatelet therapy for about 2 years, and to less than five major hemorrhages.

The question arises as to whether antiplatelet drugs increase the risk of aneurysm rupture, and, in the event of rupture, if the outcome is worse. There is no high-level evidence that antiplatelet drugs increase the risk of aneurysm rupture, or that the outcome is worse if the aneurysm ruptures. Given the shared risk factors (smoking, hypertension, age, among others) and the prevalence of unruptured aneurysms in the general population, it is likely that there are a substantial num-

<table>
<thead>
<tr>
<th>Unruptured Aneurysms: Location</th>
<th>&lt;7 mm</th>
<th>7–12 mm</th>
<th>13–24 mm</th>
<th>≥ 25 mm (giant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavernous/carotid</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>ACA/MCA/ICA</td>
<td>0–1.2%</td>
<td>2.6%</td>
<td>14.5%</td>
<td>40%</td>
</tr>
<tr>
<td>Posterior communicating or posterior circulation</td>
<td>2.5–3.4%</td>
<td>14.5%</td>
<td>18.4%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Abbreviations: ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery.
number of patients currently on antiplatelet drugs with undiagnosed, unruptured aneurysms. Several small series report patients presenting with ischemic stroke who are found to have aneurysms. In one series, there were no ruptures among 16 patients with ischemic stroke and unruptured aneurysms who were followed for 3 months on antiplatelet drugs. There were 90 (3%) of 2,885 patients in the North American Symptomatic Carotid Endarterectomy Trial with unruptured intracranial aneurysms. Eighty-two were followed for a mean of 5 years. One patient died of myocardial infarction 6 days after carotid endarterectomy, and the autopsy showed an SAH, but there was no evidence that the aneurysm was the source. Best medical management in these patients included aspirin, so it is likely that this is a cohort of patients with unruptured aneurysms who were on antiplatelet drugs for years with no SAH.

Numerous studies examined acetylsalicylic acid use in patients admitted to the hospital with an SAH. One study of 305 patients admitted with an SAH found that 29 gave a history of acetylsalicylic acid use. There was no difference in outcomes between the two groups, suggesting that treatment of patients with unruptured aneurysms who then had an SAH would be no different from those not on acetylsalicylic acid. Limitations of the data included the lack of information on patients who died without being admitted to the hospital. The authors opined on the use of antiplatelet drugs in patients with unruptured aneurysms and could offer no compelling evidence against their use if medically indicated. The risk of stroke, other morbidity, and death without antiplatelet drugs needs to be considered, but it is likely that the balance will be in favor of treating many patients with unruptured aneurysms with antiplatelet drugs when they are indicated for medical reasons. Many people take acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs for minor health problems or for perceived beneficial effects on vascular disease and stroke when no benefit exists. Patients with unruptured aneurysms probably should be advised to avoid these drugs unless there is a specific medical indication for them.

Several studies examined the efficacy of acetylsalicylic acid and other antiplatelet drugs for preventing delayed ischemia and improving outcome in patients with an SAH. Meta-analysis of the first five randomized, placebo-controlled trials found that the overall risk of poor outcome was 0.87 (95% CI, 0.65–1.17), and of delayed cerebral ischemia (DCI, reported in three of the five studies), 0.65 (95% CI, 0.47–0.89). The drugs used included acetylsalicylic acid, the thromboxane synthetase inhibitor OKY-046, and dipyridamole. This finding suggested that a larger randomized trial was warranted, but that study was stopped early when the chances of detecting a beneficial effect were statistically negligible. The question arises as to whether to stop antiplatelet drugs when a patient is admitted with an SAH. In general, this is done, given the lack of obvious clinical benefit for being on these drugs after an SAH and the lack of any documented prothrombotic state when stopping them.

Anticoagulants and Aneurysms

Anticoagulants, such as warfarin, increase the risk of fatal or disabling intracranial hemorrhage 1.5 times; intracranial hemorrhage causes 90% of warfarin-related death. The risk of intracranial hemorrhage while on anticoagulants is 0.3 to 1% per year and is increased compared with the untreated population by 0.2% per year. The outcome from anticoagulant-associated intracerebral hemorrhage (ICH)
is worse than after spontaneous ICH.\textsuperscript{25} Mortality was 33\% within 1 day compared with 16\% in those not taking anticoagulants, and 66\% versus 50\% at 1 year.\textsuperscript{25}

A study of 1,188 hospital admissions for SAH compared with 11,880 controls found no association between the risk of an SAH and anticoagulants. The study did not include deaths before admission, so it is still possible that anticoagulation increases the risk of a fatal SAH. Rinkel et al\textsuperscript{26} identified 15 patients admitted to the hospital with an aneurysmal SAH who had been taking anticoagulants. The relative risk of poor outcome was 1.9 times higher compared with 126 control patients with an aneurysmal SAH.\textsuperscript{26} The study excluded patients on anticoagulants who had an international normalized ratio (INR) < 1.5. Thus, anticoagulants, when administered at a dose that is therapeutic, worsen the outcome from an SAH, but whether they increase the risk of it occurring is less clear and not documented in the literature.

If anticoagulation is indicated in a patient with an unruptured aneurysm, this information should be taken into account because, depending on the risk of ischemic stroke if the patient were not on anticoagulants, the balance might tip in favor of treating the unruptured aneurysm before initiating anticoagulation. Decisions will be individualized in these cases because many of these patients are elderly and have factors that increase the risk of treatment of the aneurysm.

There also is no information to inform decisions about how to manage patients with unruptured aneurysms who require prophylactic anticoagulation, for example, when undergoing other surgical procedures like joint replacements. Although the risk of anticoagulant-associated ICH is higher when anticoagulants are first started, the duration of treatment in such cases is shorter. If a patient with an unruptured aneurysm presents with an SAH, then rapid reversal of anticoagulation to achieve normal coagulation is indicated. The guidelines for reversal of anticoagulation in patients with anticoagulation-associated ICH are reasonable to use given the lack of any other information.\textsuperscript{27}

Occasionally, a patient with an unruptured aneurysm may present with acute ischemic stroke and may be a candidate for thrombolytic therapy. Thrombolytic therapy increases the risk of fatal intracranial hemorrhage threefold, or 7\% of patients treated, but improves the chances of a good outcome to a greater degree when administered within 4.5 hours of the onset of stroke in appropriate patients.\textsuperscript{28} Another relevant statistic is that intracranial hemorrhage occurs in 0.3 to 1\% of patients treated with thrombolytics for myocardial infarction.\textsuperscript{29} A review of the literature up to 2004 found seven cases of patients with unruptured aneurysms treated with intraarterial or intravenous urokinase or tissue plasminogen activator. One aneurysm ruptured (14\%) and the patient died. The authors concluded that therapeutic decision making in this situation was difficult, and that physicians may often avoid using thrombolytic therapy in patients with known aneurysms, although the evidence to support this practice is lacking, and it is possible that patients with small or treated aneurysms are candidates for treatment.

### Unruptured Arteriovenous Malformations

Arteriovenous malformations (AVMs) are responsible for 1 to 2\% of all ICHs and have an annual risk of hemorrhage of 2 to 4\%.\textsuperscript{30,31} The outcome after a first hemorrhage is better than after an aneurysmal SAH or spontaneous primary ICH, with death occurring in 10\% and permanent morbidity in 30\%.\textsuperscript{31,32} Rebleeding is believed to be more common in the year after hemorrhage, occurring in 6\% of cases.
and then declining to a baseline of 2 to 4%. Emerging evidence, however, suggests the risk of hemorrhage depends on a variety of factors (Table 19.2). Multivariable analysis of 622 consecutive patients with AVMs from a prospective database found that hemorrhage was associated with increasing age, initial presentation with hemorrhage, deep location of the AVM, and exclusive deep venous drainage. The risk of hemorrhage varied from 0.9% per year for patients with no history of hemorrhage and a non-deep location with no exclusive deep venous drainage, to 34% for patients with all three risk factors. Da Costa et al studied a prospective cohort of 678 patients with AVMs. The annual risk of hemorrhage overall was 4.6%, compared with 7.5% for those presenting with hemorrhage, 4% for those presenting with seizures, 4% for those with no aneurysms, and 6.9% for those with aneurysms. Presentation with hemorrhage was significantly associated with the future risk of hemorrhage, and associated aneurysm or deep venous drainage showed trends toward this association. Other studies have suggested an increased risk of hemorrhage in patients with single draining veins, venous outflow stenosis, hypertension, and associated aneurysms. AVMs are associated with three types of aneurysms. There are flow-related aneurysms on arteries supplying the AVM in 11%, intranidal aneurysms in 6%, and aneurysms located on arteries not supplying the AVM in 1%.

There is a lack of epidemiological studies investigating anticoagulant and antiplatelet use, and bleeding rates in patients with AVMs. In general, we recommend that they avoid taking these drugs. Again, this has to be balanced against the indication for the drug, the risk of stroke, vascular events, and death if the drug is not taken, and the risk reduction achieved if the drug is taken. The most common situation would be the elderly patient in whom antiplatelet drugs are indicated for vascular disease. It is likely that in most cases the risks and benefits would favor treating such patients with these drugs if they had an untreated or untreatable AVM.

As with other types of intracranial hemorrhage secondary to vascular lesions, if a patient with an AVM presents with a hemorrhage while on anticoagulants, then rapid reversal of anticoagulation to achieve normal coagulation is indicated. The guidelines for reversal of anticoagulation in patients with anticoagulation-associated ICH are reasonable to use given the lack of any other information.

### Cavernous Malformations

Cavernous malformations (CMs) are low-flow, low-pressure vascular malformations characterized pathologically by thin-walled vascular channels with collagenous walls and endothelial cell linings. The channels are of varying size and contain blood or in some areas thrombus of varying degrees of organization. There is no intervening brain tissue and the brain around the lesion usually shows gliosis and contains hemosiderin-laden macrophages. They are found in 0.5% of adults.

#### Table 19.2 Annual Rates of Hemorrhage for Subtypes of Arteriovenous Malformations

<table>
<thead>
<tr>
<th>Nidus, not deep</th>
<th>Deep Venous Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>3%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Cavernous Malformations

Cavernous malformations (CMs) are low-flow, low-pressure vascular malformations characterized pathologically by thin-walled vascular channels with collagenous walls and endothelial cell linings. The channels are of varying size and contain blood or in some areas thrombus of varying degrees of organization. There is no intervening brain tissue and the brain around the lesion usually shows gliosis and contains hemosiderin-laden macrophages. They are found in 0.5% of adults.
Genetic linkage studies have identified three loci for CMs; CCM1 (Krev interaction trapped 1 [KRIT1]) on 7q21–22, CCM2 (MGC4607 or malcaverin) on 7p13–15, and CCM3 (programmed cell death 10 [PDCD10]) on 3q25.2–27. About 75% of familial cases have identified abnormalities in these genes, whereas mutations are identified in fewer sporadic cases. Fifty percent to 75% percent of patients with familial CM have multiple lesions compared with 15% of patients with sporadic CM. The annual risk of clinically significant first hemorrhage from CM is 0.1% to 2.7% per lesion. The annual risk of rebleeding after the first episode of hemorrhage is 4.5%, and there may be clustering of hemorrhages interspersed with periods of quiescence. An increased risk of hemorrhage has been associated with prior hemorrhage, deep or brainstem location, and possibly female sex.

As with AVMs, there are no epidemiological studies investigating anticoagulant and antiplatelet use and bleeding rate in patients with CMs. We found one case report of a 42-year-old woman with familial CM who developed hemorrhage during treatment with prophylactic low molecular weight heparin after undergoing a hysterectomy. She survived and did not suffer permanent morbidity. The authors cautioned against drawing any conclusions about the relative risks of anticoagulant drugs in patients with CM. We recommend advising patients with CMs to avoid taking anticoagulant or antiplatelet drugs unless there is a specific medical indication, in which case the risks and benefits should be reviewed and assessed on a case-by-case basis. The low risk of hemorrhage and of morbidity and mortality from hemorrhage from CMs is an important consideration in such decisions.

If a patient presents with symptomatic hemorrhage from a CM, rapid reversal of anticoagulation to achieve normal coagulation is indicated. The guidelines for reversal of anticoagulation in patients with anticoagulation-associated ICH are reasonable to use given the lack of any other information.

**Intracerebral Hemorrhage**

Chronic hypertension causes 50 to 70% of ICHs. Cerebral amyloid angiopathy is believed to be the cause in 10% of all cases and in up to 30% of lobar hemorrhages in the elderly. Rupture of vascular malformations is the etiology in 5 to 13% and is more common in younger patients. Congenital or acquired coagulopathies, the latter most commonly due to anticoagulant drugs, are the fourth most common cause, accounting for 5 to 6% of all cases of ICH. Recurrence of ICH has been associated with lobar location, increased age, use of anticoagulants, apolipoprotein E types 2 and 4, alleles, and microhemorrhages on T2*-weighted gradient echo magnetic resonance imaging (MRI). Anticoagulant-related ICH is more likely with increasing age, prior ischemic stroke, hypertension, leukoaraiosis (also known as nonspecific white matter changes), within the first months of starting anticoagulants, and if the INR is higher.

The emergency management of patients taking anticoagulants who present with ICH includes reversing anticoagulation as quickly as possible with prothrombin complex concentrates or fresh frozen plasma and intravenous vitamin K. In patients with ICH who are taking antiplatelet drugs, platelet transfusions were considered investigational. Hematoma growth is noted in up to 38% of patients with ICH when computed tomography (CT) scans can be compared within 1 hour and then within 3 hours of onset. Growth is observed in 16% of those who are first imaged between 3 and 6 hours, and 10 to 15% show hematoma enlargement.
between 6 and 24 hours from onset of ICH. Risk factors for hematoma growth include early presentation, a spot sign on CT scan, larger initial ICH, use of anticoagulants, presence of intraventricular hemorrhage, and reduced platelet activity.

There are two questions that arise concerning the patient with ICH: whether to start or resume anticoagulation, and if so, when.

### Whether to Start or Resume Anticoagulation After ICH

There is some information available on which to base decisions regarding starting an anticoagulant or antiplatelet agent in a patient with ICH related to oral anticoagulants. Most of these patients have anticoagulant-associated ICH, because it is in these cases that the question of whether to resume treatment usually arises. These patients are most commonly taking anticoagulants for atrial fibrillation and mechanical heart valves. The only other common situation is when a patient with ICH develops a deep vein thrombosis (DVT) or pulmonary embolism.

There are very few data on the risk of recurrent ICH when a patient with anticoagulant-associated ICH is restarted on anticoagulants. There are studies on the baseline risk of recurrent ICH. Follow-up of 243 patients who were able to return home after a first ICH and were followed for a mean of 5.5 years found the risk of recurrent ICH after a first hemorrhage was 1% in the first 3 months. The risk of recurrence was 2.1% per year, and higher with increasing age and male sex. If the patient was treated with anticoagulants, which usually was done for prosthetic heart valves, atrial fibrillation, or arterial occlusive disease in this study, the risk of recurrent ICH tripled. A systematic review of the literature found that spontaneous, primary lobar hemorrhages, which are often seen in the elderly and are attributed to amyloid angiopathy, have a higher risk of recurrence, probably 4% per year.

Claassen et al followed 55 patients with anticoagulant-associated ICH. Anticoagulation was restarted 7 to 28 days after ICH in 23 patients, 10 of whom had mechanical heart valves. Mortality during follow-up was not significantly different from that in patients in whom anticoagulation was not restarted. After a mean follow-up of 43 months, there were three fatal and two nonfatal hemorrhages in the restarted group, compared with no hemorrhages and one fatal and four nonfatal thromboembolic events. Other studies are small case series included in systematic reviews. Claassen and colleagues concluded that anticoagulation could be resumed in some cases and the clinician should consider the patient’s risk of falls, general medical condition, and risk factors for systemic hemorrhage.

American Heart Association guidelines on patients with heart valves have not addressed the issue of resuming anticoagulation after ICH. There are at least three systematic reviews addressing whether to resume anticoagulation in patients with anticoagulant-associated ICH. One review found seven publications (one epidemiologic study and six case series) describing 42 patients treated with anticoagulants for at least 6 months after ICH. These patients had four recurrent ICHs and nine thromboembolic events. The authors concluded that there was insufficient data upon which to base any decisions. Balancing the risk of thromboembolic events without treatment, for which there are data, with the risk of recurrent ICH after restarting anticoagulants is impossible because there are no data on the latter. The second systematic review included more studies and numerous case reports in addition to the case series because it included all types of intracranial hemorrhage and investigated whether it was safe to resume anticoagulation in patients with mechanical heart valves. But the overall quality of the data was judged to be poor. Among case series, anticoagulants were stopped for 2 days to 3
months. During a mean follow-up of 8 months, there were four ischemic strokes and two hemorrhages (one fatal). Among 18 case reports, there were two hemorrhages (one fatal) and no ischemic strokes. The authors concluded that stopping anticoagulation for a few days (and even 7 to 14 days) was safe and that resuming anticoagulation also was safe. According to commonly used evidence-based medicine guidelines, these conclusions would be very weak, but resuming anticoagulation in patients with mechanical heart valves does seem to be common practice. Another consideration is that the risk of stroke and thromboembolic events in patients with mechanical heart valves varies depending on the location and type of valve. The risk is higher for mechanical rather than tissue valves, higher for mitral than aortic valves, and higher if there is associated atrial fibrillation (Table 19.3).

Overall, the risk of valve thrombosis and major or minor embolic events is 9 to 22% per year. Long-term anticoagulation is most commonly indicated for nonvalvular atrial fibrillation. In these patients, the risk of ischemic stroke is 2 to 5% per year but is stratified based on several different grading systems. One is the CHADS$_2$ scoring system (Table 19.4). Risk of ischemic stroke varies from 2% per year in patients

### Table 19.3 Estimates for Risk of Thromboembolic Events for Various Cardiac Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Annual Risk of Thromboembolic Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioprosthesis aortic valve</td>
<td>0.5–2%</td>
</tr>
<tr>
<td>Bioprosthesis mitral valve</td>
<td>0.4–4%</td>
</tr>
<tr>
<td>Mechanical aortic valve</td>
<td>0.3–4%</td>
</tr>
<tr>
<td>Mechanical mitral valve</td>
<td>0.5–8%</td>
</tr>
<tr>
<td>Intracardiac thrombus</td>
<td>3–15%</td>
</tr>
</tbody>
</table>

### Table 19.4 CHADS$_2$ Score to Predict Risk of Stroke in Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Points</th>
<th>Annual Risk of Stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Note: Patients with 1 point: congestive heart failure, hypertensive history, age >75 years, diabetes; patients with 2 points: prior ischemic stroke or transient ischemic attack.
with a score of 0, to 18% in those with a score of 6. Examining this scale suggests that in patients with prior ICH, it may not be recommended to start or resume anticoagulation for patients with atrial fibrillation and a low CHADS\textsubscript{2} score, for example, patients without prior ischemic stroke or transient ischemic attack plus at least another risk factor, or with three or four risk factors, because their risk of ischemic stroke (4% per year) is similar to the risk of hemorrhage without anticoagulants. One also has to consider that the morbidity and mortality from anticoagulant-associated ICH is higher than that from ischemic stroke. The decision to resume anticoagulation in those with more risk factors for stroke would be made on a case-by-case basis.

Attempts to model this determination with decision analysis have been made, but the data to base the models on, as noted above, are poor or nonexistent. One decision analysis found that anticoagulation after anticoagulation-induced ICH could seldom be recommended, except perhaps in a patient with deep ICH, controlled hypertension, and a high risk of thromboembolic events. The indications have to be extremely compelling in patients with lobar ICH or microhemorrhages on MRI, because these patients often have amyloid angiopathy and are at higher risk of recurrent ICH (4 to 15% per year) without anticoagulants. These recommendations are consistent with those in American Heart Association guidelines for management of ICH. Those guidelines state that patients with nonvalvular atrial fibrillation and lobar ICH should probably not be restarted on anticoagulants (class 2a, level B evidence) and that anticoagulation may be considered after nonlobar ICH when there are definite indications for anticoagulation (class 2b, level B evidence).

It is important to control risk factors—such as hypertension, diabetes, and smoking—for vascular disease in all cases. There should be no indication of recurrent ICH on repeat CT scans. Patients generally should be started on unfractionated heparin without a bolus, or preferably a low molecular weight heparin and then bridged to warfarin. A lower target INR goal of 2 might also be considered.

When to Start or Resume Anticoagulation After ICH

If a decision is made to start or resume anticoagulation, when is it safe to do so after ICH? Wijdicks et al\textsuperscript{56} retrospectively reviewed 39 patients with mechanical heart valves and ICH, subdural hemorrhage, or subarachnoid hemorrhage. Only eight of 26 actually had increased prothrombin times at the time of ICH. Anticoagulation was stopped for 2 days to 3 months (mean of 8 days), and no patient suffered a thromboembolic complication during this time. One patient with bilateral acute subdural hematomas presented 3 years later with an ICH, but the prothrombin time was normal on that admission. The authors suggested that one could resume anticoagulation 1 to 2 weeks after ICH with or without craniotomy. Another series suggested resuming anticoagulation 3 days after craniotomy for ICH.\textsuperscript{57} Another study reviewed 141 patients with anticoagulant-associated ICH, subdural hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage, and an estimated high risk of thromboembolic events due to mechanical heart valves, atrial fibrillation, recurrent stroke, or transient ischemic attack.\textsuperscript{58} Anticoagulation was stopped for 0 to 30 days (median of 10 days). The risk of thromboembolic events was 3 to 5% within the first 7 days in all groups. The authors recommended stopping anticoagulation for 1 to 2 weeks before resuming it, if the decision was made to resume it. Tinker and Tarhan\textsuperscript{59} stopped anticoagulation for a mean of 7 days
in 180 patients with mechanical heart valves who were undergoing various surgeries.\textsuperscript{59} There were no thromboembolic complications.

Numerous studies show that in general anticoagulation can be stopped for days with a low risk of thromboembolic events.\textsuperscript{60} These reports include patients taking anticoagulants for varying indications who develop different types of intracranial hemorrhages, although the most common indications are for atrial fibrillation and heart valves. One series of 108 patients with ICH or subdural hemorrhage while on anticoagulants found that the risk of thromboembolic events while anticoagulants were stopped was 0.66 events/1,000 patient days.\textsuperscript{60} Seven of eight recurrent hemorrhages were before anticoagulants were resumed, and the one hemorrhage after starting anticoagulants was after 4 months in a patient with a chronic subdural hematoma.

Another review that focused on resuming anticoagulation after neurosurgery classified patients as high, medium, or low risk of recurrent thromboembolic events.\textsuperscript{52} High-risk patients included those with high-risk peripheral vascular grafts within 9 months of bypass, recent arterial thromboembolic events, or intracardiac thrombi. These authors stopped anticoagulants for intracranial surgery, treated the patient with subcutaneous low-dose heparin postoperatively, and resumed anticoagulation with heparin (no bolus) followed by warfarin 3 to 5 days after surgery. Moderate-risk patients included mainly those with mechanical mitral or combined valves, valvular atrial fibrillation, atrial fibrillation with a recent thromboembolic event, and patients with older peripheral vascular grafts. These patients were treated with low-dose subcutaneous heparin postoperatively and then started on anticoagulation 5 to 7 days after surgery. In the low-risk group of patients with more chronic atrial fibrillation, aortic valve replacements, bioprosthetic mitral valves, and such, again low-dose subcutaneous heparin was administered postoperatively and anticoagulation resumed 7 to 14 days after surgery.

A systematic review found several case series and case reports in which anticoagulants were stopped for 2 days to 3 months after various types of intracranial hemorrhage.\textsuperscript{48} Most physicians stopped anticoagulants for 7 to 14 days.

A third systematic review included all types of intracranial hemorrhage.\textsuperscript{51} The authors noted that most recurrent intracranial hemorrhage occurred within 3 days of the first hemorrhage, and most thromboembolic events occurred later than 3 days.\textsuperscript{51} Only 13\% of patients were on anticoagulants when they rebled, and patients with subdural hematoma were more likely to rebleed. The authors concluded that it might be reasonable to resume anticoagulation, if indicated, more than 3 days but earlier than 7 days after ICH, which is sooner than generally done.

For patients with mechanical heart valves, the overall risk of thromboembolic events was in the worst case scenario estimated to be 10 to 20\% per year.\textsuperscript{49,50} In the American Heart Association guidelines, it is generally recommended to stop anticoagulation for 3 days in patients with mechanical valves who are undergoing surgery. The risk of a thromboembolic event during this time would be 0.08 to 0.16\%. The guidelines do not address intracranial surgery or patients with ICH.

**Venous Thromboembolism Prevention and Treatment for Patients with Intracerebral Hemorrhage**

Rarely, a patient with an unruptured aneurysm or known brain vascular malformation develops venous thromboembolic disease. More commonly, patients admitted with ICH develop venous thromboemboli and are candidates for anticoagulation.
The first issue to decide is the use of prophylactic treatment in these patients. The American College of Chest Physicians’ 2008 anticoagulation guidelines give evidence-based practice guidance on venous thromboembolism prophylaxis for patients with ICH. The guidelines recommend the initial use of intermittent pneumatic devices (grade 1B evidence) and that in stable patients, with no indication of hematoma growth, low-dose subcutaneous heparin can be safely started as early as the second day after hemorrhage (grade 2C evidence). American Heart Association guidelines on the management of ICH reported that intermittent pneumatic compression combined with elastic stockings was superior to elastic stockings alone in reducing occurrence of asymptomatic deep vein thrombosis after ICH in one randomized trial (4.7% versus 15.9%). Graduated compression stockings by themselves were of no use. Whether to add pharmacological prophylaxis to mechanical compression methods has been studied in patients with ICH, but the studies are small and did not find any differences in the incidence of deep vein thrombosis or bleeding. The guidelines concluded that after ICH, patients should have intermittent pneumatic compression plus elastic stockings (class 1, level of evidence B). The recommendation for starting pharmacological prophylaxis was the same as other guidelines, in that once there was no evidence of ongoing intracranial bleeding, low-dose subcutaneous low molecular weight or unfractionated heparin could be considered in patients with ICH who were immobile, beginning 1 to 4 days after the ICH (class 2b, level of evidence B).

In neurosurgery patients undergoing craniotomy, a meta-analysis was conducted of eight randomized clinical trials comparing low-dose unfractionated or low molecular weight heparin with controls for prevention of venous thromboembolism after surgery. Although the risk of venous thromboembolism was nearly halved with pharmacological prophylaxis, the risk of hemorrhage was increased as well, making decision making complex. In patients with unruptured aneurysms and vascular malformations who require short-term perioperative pharmacological prophylaxis, the benefits would generally outweigh the risk of hemorrhage.

There is lack of available evidence regarding optimal treatment of venous thromboembolism in patients with acute ICH. We, therefore, rely on the following observations. In patients with acute ICH, the risk of fatal pulmonary embolus is 25% for those with an untreated proximal deep vein thrombosis. On the other hand, the risk of recurrent ICH while on anticoagulants is 3 to 5% (three- to fivefold risk over placebo). Hence, treatment with anticoagulants is justified as the risk of fatal pulmonary embolism is high. Unfractionated heparin and low molecular weight heparins are highly efficacious and could be started days after ICH, and then the patient bridged to reduced doses of oral anticoagulation (with a target INR of 2.0) for 3 to 6 months. Pharmacological prophylaxis could be continued with serial imaging to rule out extension in patients with deep vein thrombosis below the knee. Placement of vena cava filters is a reasonable option in patients judged to be at high risk of rebleeding after ICH, intracranial surgery, or rupture of a vascular lesion.

**Antiplatelet Drugs and ICH**

Data are conflicting on whether patients taking antiplatelet drugs have a higher risk of primary ICH, or have a poorer outcome if they have ICH compared with those not taking these drugs. Measurement of platelet function showed a poor correlation between the reported use of antiplatelet drugs and platelet function in
patients with ICH, suggesting that the history may be unreliable and that this could explain the difficulty in showing correlations among antiplatelet use, ICH expansion, and outcome. Analyses of randomized clinical trials found minimal or no effect of prior antiplatelet use on ICH expansion after hospital admission. The utility of platelet transfusion in patients admitted with an ICH associated with antiplatelet use was considered investigational in recent ICH guidelines. Exploratory observations on use of acetylsalicylic acid from the International Stroke Trial and Chinese Acute Stroke Trial found 773 patients were randomized to aspirin or placebo before they had a CT scan showing that they had an ICH rather than an ischemic stroke. This was not associated with an increased risk of death. These data are not very useful when considering whether to start antiplatelet drugs after ICH because they are not population-based, and patients on antiplatelet drugs who die or are not treated are not entered into these studies, which could underestimate the risks.

There is one study addressing the use of antiplatelet therapy in patients with prior ICH; 207 patients who survived an ICH were followed for a median of 20 months, 46 of whom (22%) were treated with antiplatelet drugs. There were 32 recurrent ICHs (20%) among 161 patients who did not receive antiplatelet drugs and seven ICHs (15%) among the 46 who did. Ischemic cardiovascular events occurred in seven untreated and four treated patients. Overall, there were no significant differences in risk of recurrent lobar ICH in patients on antiplatelet drugs (hazard ratio [HR], 1.2; 95% CI, 0.4–3.3) or risk of deep ICH (HR, 1.2; 95% CI, 0.1–14.3) or ischemic events (HR, 1,2; 95% CI, 0.3–4.8). Experts have conflicting opinions about these data. Some note that the confidence intervals are wide, which suggests that antiplatelet drugs should only be administered after ICH in patients at high risk of ischemic events, and that more data are needed. Others consider this study more definitive, that antiplatelet drugs do not increase the risk of recurrent ICH and that they should be administered if otherwise indicated.

One approach is to resume or start acetylsalicylic acid at a low dose (81 mg/d) in patients with strong indications, such as clinically important coronary artery disease or atrial fibrillation. The indications have to be increasingly compelling in patients with lobar ICH or microhemorrhages on MRI, because these patients often have amyloid angiopathy and are at higher risk of recurrent ICH (4 to 15% per year) without antiplatelet drugs. The indication for antiplatelet drugs could be weaker in patients with deep ICH, where the risk of recurrence is lower (2% per year). It is important to control risk factors for vascular disease in all cases, such as hypertension, diabetes, and smoking. The American Heart Association guidelines on management of ICH state that antiplatelet therapy after lobar or deep ICH can be considered when there are definite indications for these drugs (class 2b, level of evidence B).

**KEY POINTS**

- The decision regarding the use of anticoagulant and antiplatelet agents in patients with concomitant neurovascular conditions is made in the following way: the best available estimate of the natural risk of hemorrhage in that condition is weighed against the best estimate of the risk of the event that the agent is meant to prevent. Added to that, as always in neurosurgery, is the consideration of the lesion location and the possibility of catastrophic consequences from worsening the severity of any hemorrhage in that location.
Defects in platelet activity or in coagulation factors (coagulopathy) or both lead to a prolonged bleeding time.

A prolonged prothrombin time can be caused by warfarin, vitamin K deficiency, liver dysfunction, congenital factor VII deficiency, or mild DIC.

A prolonged activated partial thromboplastin time can be caused by heparin, lupus anticoagulant, deficiencies of factors VIII, IX, or XI, and von Willebrand disease.

A prolonged thrombin time can be caused by fibrinogen abnormalities and inhibitors of the conversion of fibrinogen to fibrin, the final step of the coagulation cascade.

The best available evidence supports the conclusion that aspirin does not increase the risk of rupture in patients with unruptured aneurysms. Patients with known aneurysms, however, should be counseled to avoid antiplatelet agents unless it is likely that their risk of stroke, vascular, or cardiac event is higher than their estimated risk of aneurysm rupture.

In general, patients with arteriovenous malformations (AVMs) should avoid taking antiplatelet and anticoagulant medications. The exceptions would include patients with untreatable AVMs who have a high risk of morbidity from stroke, cardiac ischemic disease, or other vascular disease, or of death.

Patients with cavernous malformations (CMs) should be counseled to avoid antiplatelet and anticoagulant medications unless there is a compelling medical indication for their use. As opposed to AVMs and aneurysms, however, the low risk of hemorrhage and the generally low mortality of hemorrhage from CMs will figure importantly in the risk/benefit analysis.

Patients on anticoagulants who present with aneurysm rupture or symptomatic hemorrhage from an AVM or cavernous malformation should have their anticoagulation reversed along the guidelines used for anticoagulation-associated intracerebral hemorrhage (ICH).

The decision to restart anticoagulation after ICH remains a difficult one because of the lack of quality evidence. Patients with nonvalvular atrial fibrillation or patients with lobar ICH should probably not be restarted on anticoagulants because of the high risk of recurrent ICH. Patients with nonlobar ICH and strong indications for anticoagulation should be considered candidates for restarting anticoagulation. The timing of restarting anticoagulation remains controversial, and should be based on the perceived risk of a thromboembolic event.

Resumption of antiplatelet drugs in patients with ICH can be considered in those at low risk for recurrent ICH, specifically nonlobar hemorrhage and no evidence on MRI of microhemorrhages associated with amyloid angiopathy.

Prophylaxis of venous thromboembolic events in patients with ICH is an emerging field of study. Many centers begin pharmacological prophylaxis with low molecular weight or unfractionated heparin 1 to 4 days after ICH, provided there is no evidence of ongoing hemorrhage. Inferior vena caval filters remain a reasonable option in patients judged to be at high risk of recurrent hemorrhage or after rupture of a vascular lesion.
REVIEW QUESTIONS

1. A patient with a prolonged prothrombin time found preoperatively may have all of the following except:
   A. A diet poor in vitamin K content
   B. Chronic cirrhosis
   C. Von Willebrand disease
   D. Congenital factor VII deficiency

2. Reliable class 1, level A evidence from randomized trials supports which of the following statements:
   A. The risk of aneurysm rupture is increased in patients with coronary artery disease who take aspirin for prophylaxis against cardiac events.
   B. The risk of stroke is decreased for patients with atrial fibrillation who do not tolerate warfarin if they take aspirin instead.
   C. Thrombolytic therapy should be avoided in patients with known unruptured aneurysms presenting within an hour of an acute ischemic stroke who would otherwise be candidates for thrombolysis.
   D. Patients with known cavernous malformations but a high risk for stroke from an untreated intracranial stenosis should avoid antiplatelet medications.

3. Increased risks for recurrence of intracerebral hemorrhage include all of the following except:
   A. Lobar location of hemorrhage
   B. Presence of microhemorrhage on T2*-weighte gradient echo imaging
   C. Increased age
   D. Deep location of hemorrhage
   E. Use of anticoagulants

4. Risk factors for hematoma growth in the first 24 hours after intracerebral hematoma include all of the following except:
   A. “Spot sign” on CT imaging
   B. Absence of intraventricular hemorrhage
   C. Reduced platelet activity
   D. Use of anticoagulants
   E. Early presentation

5. A patient on warfarin anticoagulation for atrial fibrillation and demonstrated intracardiac thrombus presents with a small, nonlobar intracerebral hemorrhage and well-controlled hypertension. True or false: It is reasonable to consider restarting anticoagulation in this patient.

References


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<thead>
<tr>
<th>ANSWER KEY</th>
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<tbody>
<tr>
<td>1. C</td>
</tr>
<tr>
<td>2. B</td>
</tr>
<tr>
<td>3. D</td>
</tr>
<tr>
<td>4. B</td>
</tr>
<tr>
<td>5. True</td>
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</table>
Ischemic Stroke Diagnosis and Management

Michael D. Hill

Stroke is a major public health illness that is debilitating and expensive.\textsuperscript{1,2} It requires a team approach to treatment. This team includes a neurologist or stroke specialist, a neurosurgeon, a neuro-interventional, a stroke physiatrist, a stroke nurse specialist, a physiotherapist, an occupational therapist, a speech-language therapists, a social worker, and many others. In-hospital stroke care takes place in the stroke unit. Although in most hospitals the stroke units are organized and run by medical specialties (neurologists, geriatricians, internists), the neurosurgeon has a critical role to play in the stroke team. This chapter discusses introductory information on ischemic stroke, and provides basic information on the medical care of the stroke patient in-hospital and through rehabilitation and outpatient management of secondary prevention. It focuses on the neurosurgical aspects of stroke care.

What Is a Stroke? How Common Is Stroke? What Are the Major Risk Factors?

Stroke is a sudden vascular syndrome of the brain and can be of four types: ischemic stroke (includes transient ischemic attack [TIA]), intracerebral hemorrhage, spontaneous subarachnoid hemorrhage (SAH), and venous sinus thrombosis. Ischemic forms are the most common; acute ischemic stroke and TIA make up 85% of all strokes in the Western World and 10 to 15% fewer in Asia due to a greater predominance of intracerebral hemorrhage. Intracerebral hemorrhage and atraumatic/aneurysmal SAH make up 15% of all strokes, and venous sinus thrombosis make up less than 1% of all strokes. Ischemic stroke should be thought of as a continuum from the mildest, transient forms—TIA—to the most severe, malignant middle cerebral artery (MCA) syndromes. Ischemic stroke is the end result of a multiplicity of possible underlying causes and shows an exponential incidence with increasing age. By the age of 80 years, one in four persons will have suffered a stroke.

Epidemiologically, stroke is not well characterized by its incidence or prevalence because it is an episodic condition that has multiple underlying causes. Rates are best described as events or occurrences. First-ever stroke is the best surrogate term for incident stroke. Prevalent stroke is not a meaningful term and should be avoided. Over the last half century, the age-adjusted occurrence of stroke has been slowly falling. Stroke now occurs at 150 per 100,000 population in Canada,\textsuperscript{3} which means that within a given population of 1 million persons, it is expected that there will be 1,500 strokes per year. Rates are similar in other Western countries. Stroke mortality has been similarly falling.\textsuperscript{4} Although stroke is the second leading cause of death internationally, it has dropped to fourth leading cause of death in North
Nevertheless, with a progressively aging population in the developed world, the total number of strokes and hence the burden on health systems is going to rise substantially over the next 25 years.

The most important risk factor, quantitatively, for stroke of all types is hypertension. Ischemic stroke risk factors vary by stroke mechanism. We can think of risk factors, such as hypertension and risk states, such as carotid artery stenosis. Ischemic stroke can be broadly defined by the mechanism based on the presumed immediate cause of the stroke. There are five groups of causes: (1) cardioembolic, (2) large artery atherosclerotic disease, (3) lacunar or small vessel disease, (4) other uncommon causes, and (5) cryptogenic or unknown cause.

Atherosclerotic risk factors include hypertension, diabetes mellitus, smoking, excessive alcohol consumption, elevated cholesterol or other hyperlipidemia, obesity, physical inactivity, hyperhomocysteinemia. Diet and sedentary lifestyle are important contributing factors. Hypertension is the most common risk factor for stroke with an attributable risk approaching 40%, meaning that if hypertension was eliminated, stroke occurrence would fall by 40%.

Cardioembolic stroke is caused by an embolism of thrombus from within the heart to a usually normal intracranial artery. Atrial fibrillation is the most common cardioembolic source, and thrombus in the left atrial appendage is the most common source of the thrombus, in chronic or paroxysmal atrial fibrillation. Cardioembolism arises from valvular heart disease, mural thrombus after acute myocardial infarction, paradoxically across an atrial septal defect (possibly including patent foramen ovale), and from intracardiac tumors such as atrial myxoma or fibroelastoma.

Lacunar or small vessel disease, in contrast, does imply occlusion of a small penetrating artery or arteries in the intracranial circulation. These arteries are too small to visualize adequately on conventional angiography, and so their occlusion is inferred from the small size (< 15 mm) and deep white matter location of the infarct. Lacunar infarcts are caused by (1) intrinsic disease of these small penetrating arteries, such as degenerative lipohyalinosis associated with chronic hypertension or microatheroma associated with atherosclerosis; or (2) embolic occlusion from cardioembolic or arteroembolism from large artery sources. Although intrinsic disease of the small penetrating arteries is more common, it is an error of terminology to associate all lacunar infarcts with intrinsic small-vessel disease. Patients with an acute “lacunar” infarction benefit from thrombolysis, and patients with a carotid artery stenosis and lacunar stroke benefit from carotid endarterectomy.

Finally, there are multiple varied other causes of ischemic stroke. These include blunt arterial injury after trauma, extracranial artery dissection, moyamoya syndrome, infectious causes such as herpes simplex virus or varicella zoster virus–associated vasculitis, bacterial endocarditis, metabolic stroke associated with mitochondrial disease, inflammatory conditions such as Takayasu's arteritis, and many other conditions. When stroke has been thoroughly investigated and no cause is
identified, stroke is labeled as cryptogenic. Naturally, this label must always be considered in light of the full knowledge of what kind of workup was completed.

Diagnosing Stroke

Clinical Syndromes

Acute stroke can generally be diagnosed in a straightforward manner; problems in diagnosis arise when the history is incomplete or the examination not thorough. Stroke is sudden and it is statistically the most common cause of an acute neurologic deficit in both young and old. Therefore, an acute neurologic deficit is stroke until proven otherwise.

In contrast, stroke type cannot be diagnosed clinically. A stroke syndrome is undifferentiated until imaging defines the distinction between hemorrhagic and ischemic forms. Some clinical features such as sudden headache, altered level of consciousness and signs of mass effect are more commonly associated with acute hemorrhage, but these signs do not have adequate specificity to aid in clinical decision making.

Stroke can be thought of in four clinical syndromes defined by the Bamford et al. These are the total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS), and posterior circulation syndrome (POCS), which roughly define, in order, an M1-MCA occlusion, a branch MCA occlusion, a small penetrating artery occlusion, and a posterior circulation occlusion. The definitions are as follows: (1) TACS entails a triad of hemiparesis (or hemisensory loss), dysphasia (or other new higher cortical dysfunction), and homonymous hemianopia. (2) PACS entails two of the features of TACS, or isolated dysphasia or parietal lobe signs. (3) LACS entails pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, or dysarthria-clumsy hand syndrome. (4) POCS entails brainstem or cerebellar signs, or isolated homonymous hemianopia. Stroke can be confirmed with the brain imaging provided by computed tomography (CT) or magnetic resonance imaging (MRI).

Alternatively in the modern era, stroke is localized to the relevant artery that is occluded. The use of CT angiography in acute stroke and the evolution of endovascular therapy have made arterial localization a more relevant discriminating tool. In the era of acute stroke thrombolysis, decisions about the diagnosis and treatment must be made within a few minutes and most often with incomplete information. Thus, there is much discussion about “stroke mimics” of an acute stroke presentation, and they must be considered carefully in the differential diagnosis (Table 20.1).

Imaging

Imaging of the brain in the acute setting is typically completed with brain noncontrast CT. Attention must be paid to the quality of imaging and technical acquisition parameters of the scanner to optimize the image quality. Acute MRI is an alternate but is less readily available and is disadvantaged in the acute stroke setting by the necessary time required for imaging. CT is insensitive to small volume ischemia, whereas MRI, using echo-planar techniques to produce diffusion-weighted imaging,
<table>
<thead>
<tr>
<th>Common Stroke Mimics</th>
<th>Comments</th>
<th>Pitfalls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Todd’s paresis</td>
<td>An unwitnessed seizure leaves a patient with focal neurologic signs.</td>
<td>Ischemia can cause an acute seizure. Ensure that the patient does not have an acute arterial occlusion.</td>
</tr>
<tr>
<td>Migraine</td>
<td>Migraine with aura is a neurologic condition that results in brain dysfunction and acute symptoms.</td>
<td>There is very often a history of aura or a family history of migraine with aura. Be sure. Diffusion-weighted magnetic resonance imaging can rule out a stroke.</td>
</tr>
<tr>
<td>Somatization</td>
<td>Somatoform symptoms associated with psychological angst are very common in all cultures and ethnic backgrounds. True malingering or Munchausen syndrome presenting as stroke are rare.</td>
<td>Typically there are inconsistencies on examination. Do not be fooled. Diffusion-weighted magnetic resonance imaging can rule out a stroke.</td>
</tr>
<tr>
<td>Metabolic disturbance/</td>
<td>Multiple metabolic conditions (hypoglycemia, drug overdose, hyponatremia, systemic infection, etc.) may present with an acute focal deficit. This is particularly true when there has been previous brain injury, such as a prior stroke. In this case, the patient presents with reemergence of the prior stroke symptoms.</td>
<td>Do not be lulled into missing a basilar artery occlusion by investigating metabolic causes of coma first. Get a picture of the basilar artery with a CT angiogram.</td>
</tr>
<tr>
<td>systemic infection</td>
<td></td>
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<tr>
<td>Subdural hemorrhage</td>
<td>Subdural hemorrhage, particularly acute-on-chronic subdural, may present with sudden focal deficits.</td>
<td>Beware the isodense subdural hemorrhage, as it can be easily missed on CT.</td>
</tr>
<tr>
<td>Glioma</td>
<td>Tumors may similarly present with sudden focal deficits.</td>
<td>Imaging is needed to identify a glioma.</td>
</tr>
<tr>
<td>Dementia</td>
<td>Patients with advanced dementia may present with sudden focal neurologic syndromes. These may have an underlying metabolic cause, but often the cause is not determined.</td>
<td>Obtain a careful history of cognitive status.</td>
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demonstrates exquisite sensitivity of infarcts smaller than 1 mL.11 As discussed, imaging and its interpretation are critical to acute stroke diagnosis (Table 20.1).

Imaging the arteries is equally critical. CT angiography is emerging as a vitally important tool in the management of acute stroke. Rapid knowledge of the extracranial and intracranial vasculature is highly useful in making diagnostic interpretation and subsequent management decisions (Fig. 20.1).

**Treatment**

**Acute Medical Care**

Acute ischemic stroke that is disabling, that presents in a hospital setting, and that can be treated within 4.5 hours of onset should be considered for intravenous thrombolysis with tissue plasminogen activator (tPA) (Alteplase) at 0.9 mg/kg.12 It should be given as a 10% bolus dose (0.09 mg/kg IV push) and then the remaining dose (0.81 mg/kg) infused over 60 minutes.13 The critical issue with stroke thrombolysis is that it must be administered soon after stroke onset. Current guidelines in North America and Europe advise treatment with a door-to-needle time of less than 60 minutes. However, treatment within 30 minutes of arrival is possible and necessary if excellent outcomes are to be achieved.13,14 Acute ischemic stroke treatment with thrombolysis should be administered with exactly the same level of alacrity as an emergency craniotomy.

Acute management of blood pressure and glucose, and issues of general medical support are poorly defined in acute stroke. A major randomized controlled trial is examining the issue of glucose control in acute stroke—the Stroke Hypoglycemia Insulin Network Effort (SHINE) trial (Clinicaltrials.gov number NCT01369069). Blood pressure is managed based on expert opinion; no randomized trials have been done in this area.

Medical therapy subsequently should be conducted on a stroke unit.15 A stroke unit is a dedicated, geographic unit in which stroke patients are cared for by a team of experts. This team-based care is essential to the good outcomes achieved with stroke units compared with general medical wards. The team should consist of a stroke physician, stroke nursing staff, physiotherapists, occupational therapists,
speech-language therapists, a social worker, a physiatrist, and others. A team-based approach to care builds expertise. The prevention of stroke-related complications is a critical component of stroke unit care. These complications include aspiration pneumonia, venous thromboembolism (deep venous thrombosis [DVT] and pulmonary embolism [PE]), recurrent stroke and progression of stroke, and urinary tract infection. Concurrently, investigations of the stroke mechanism and risk stratification can be done, with the subsequent implementation of stroke prevention treatments, education of patients and families about the condition, and the beginning of stroke rehabilitation. Stroke units reduce hospital length of stay, reduce morbidity and mortality, and improve quality of life. Stroke units are cost-neutral in most jurisdictions compared with general medical wards.

Specific Neurosurgical Issues in Acute Stroke Care

Several specific ischemic stroke syndromes require early management and the careful judgment of the neurosurgeon.

Malignant Middle Cerebral Artery Syndrome and Decompressive Hemicraniectomy

There is strong evidence from randomized clinical trials that decompressive hemicraniectomy with duraplasty is both lifesaving and disability preventing. But this evidence pertains only to patients under the age of 60. Despite the randomized trial evidence, many questions remain about patient selection and treatment (Fig. 20.2).

Some issues are clear. Patients with a large MCA infarction should be transferred early to a neurosurgical center for observation and imaging every 12 hours. The procedure should include a wide, large hemicraniectomy, typically with a cruciate dural incision to allow brain swelling. Excision of brain tissue is not necessary or desirable. Careful postoperative nursing is required for the next 4 to 8 weeks until the bone flap can be replaced. The bone flap may be placed in cryostorage in antibiotic solution or may be placed in the peritoneum.

Fig. 20.2a-h  Brain imaging done 33 hours after the onset of stroke or later.
The patient selection criteria for this procedure remain unclear, and it is our experience that a very careful discussion with family is required. The procedure does not reverse the existing deficit; it prevents death and, possibly by reducing tissue pressure, improves microvascular circulation in the peri-infarct region. But the patient will still be left with the typically major deficits that arise from a large stroke. Key questions about the acceptability to the patient must be considered, because most patients survive this operation and move on to rehabilitation. The family must be willing to make the sacrifices necessary to accommodate a patient with severe disability. Sometimes this is acceptable and sometimes it is not. It is often more complicated when the social situation is less than ideal. Our belief is that it is a procedure that should generally not be offered to patients in the seventh decade of life or older.

Although the trials found no difference in global outcomes between left and right hemisphere hemicraniectomy, there remains a bias toward performing this procedure for malignant right MCA infarction. It remains unknown if this is reasonable or not. Our experience is that involvement of the MCA plus another territory portends a very poor outcome after this procedure. A carotid “T” occlusion with involvement of the anterior cerebral artery (ACA) territory, or, if there is a fetal-type posterior cerebral artery (PCA), involvement of the occipital lobe, implies greater brain injury and a much poorer trajectory in rehabilitation.

The optimal timing of the procedure is also poorly defined. All patients should have brain imaging completed every 12 hours during the medical management phase. Not all patients who are identified in the acute phase as possibly requiring hemicraniectomy will actually need it. Some can be managed medically; they suffer a period of brain edema and do not herniate and die. Many neurosurgeons are therefore reluctant to operate early, preferring to see evidence of compromise of the intracranial compartment before proceeding to the operating room. In the trials, patients were operated upon within 48 hours of their admission to hospital. In our view an early operative approach is highly desirable. The procedure is generally benign. The infectious risk is low, and postoperative nursing is relatively easily managed. Waiting for signs of herniation is inviting disaster. The procedure is a prophylactic one that should be done early.

**Large Inferior Cerebellar Infarction and Decompressive Suboccipital Craniecomy**

Occlusion of the fourth segment of the vertebral artery due to atherosclerotic plaque or dissection, or embolic occlusion of the posterior inferior cerebellar artery (PICA), can result in infarction of the inferior cerebellum, with or without concurrent infarction of the inferolateral medulla (Wallenberg syndrome). Where the PICA is dominant, a large infarction may occur. With the evolving vasogenic edema, the patient may suffer malignant infarction with rostral-caudal herniation of the tonsils, medullary compression, and death. The situation is exactly analogous to malignant MCA infarction.

Treatment with early suboccipital decompressive craniectomy may be lifesaving. Similar to the malignant MCA patients, all patients with the potential need for suboccipital craniectomy should be transferred to a neurosurgical center, be managed on a high observation neurologic unit, and be imaged every 12 hours during the medical management phase. Not all patients will require surgery, and observation is warranted according to the imaging. As with the malignant MCA syndrome patient, intervention is best done early with a wide craniectomy and duraplasty.
Excision of brain tissue is not required or desirable in most circumstances, except when a brain tissue excision (partial cerebellec- tomy) is required to obtain ade- quate decompression.

Patients who herniate rostrocaudally at the foramen magnum die quickly—in a few minutes. There are few warning signs clinically. Again, the intervention is a prophylactic one and is best performed early.

The placement of an external ventricular drain in this syndrome is somewhat risky and certainly controversial. There is the risk of upward herniation of the su- perior vermis of the cerebellum with compression of the mesencephalon. Further, the general problem is usually not obstructive hydrocephalus but rather focal edema at the site of infarction. Overall, our belief is that if there is a consideration of placing an external ventricular drain (EVD), then it is probably time to deal with the problem definitively and perform a suboccipital decompressive craniectomy.

**Endovascular Treatment**

Endovascular treatment for acute ischemic stroke is based on the principle that restoration of blood flow is the best way to improve outcome. The technology has rapidly developed and evolved over the past decade. Initial work with delivery of thrombolytic drugs at the site of the thrombus evolved to the use of a guidewire and microcatheter for mechanical disruption of thrombus. Subsequent innovation has led to the mechanical thrombectomy procedure with the Concentric Merci retriever (Concentric Medical, Mountain View, CA) and now a new class of sten- triever devices. In parallel, aspiration thrombectomy has been developed using the Penumbra Stroke System (Penumbra Inc., Alameda, CA) or simply a large-bore guide catheter and a 60-cc syringe.

Three recent trials have failed to demonstrate that endovascular treatment is superior to standard intravenous thrombolysis. These trials have cast a pall on the field but have rekindled equipoise regarding the role of endovascular treat- ment. Currently, some private insurers have withdrawn coverage for this procedure. But in truth these trials are only the opening foray. There were three key weaknesses to these trials: (1) suboptimal devices were used, with subsequent incomplete revascularization; (2) treatment was too slow; and (3) optimal patients for this therapy were not chosen using modern imaging techniques. New trials are being designed to assess the patient population, and it seems likely that the popu- lation to be treated will be further defined with new trials.

Endovascular treatment for vertebral artery or carotid artery sacrifice is rarely encountered in ischemic stroke syndromes. Rarely, a vertebral artery dissection will be unstable and present with recurrent thromboembolism. Coil occlusion and vessel sacrifice may be required to prevent major stroke. Similarly, pseudoaneu- rysm formation after dissection may be managed safely with vessel sacrifice.

**Open Embolectomy**

There are case reports of open craniectomy with microvascular intracranial embo- lectomy. However, with the evolution of endovascular treatments for acute ischemic stroke that are faster and less invasive, this treatment is no longer widely used. If it is to be performed in an exceptional circumstance, such as a foreign body embolism, it must be done quickly to obtain a reasonable outcome, and it requires a highly technically adept surgeon to complete the procedure in a timely fashion.
Carotid Revascularization

Optimal stroke prevention commonly requires carotid revascularization. Carotid endarterectomy (CEA) is the preferred approach for the uncomplicated patient. It is associated with a clear reduction in stroke or death as compared with carotid artery stenting.\(^{39-42}\) Among patients with poor anatomy (high bifurcation, isolated circulation), carotid artery stenting may be preferred. Carotid artery stenting may also be ideal for patients who are judged to be at high risk for a general anesthetic; however, among these high-risk patients, the reflective surgeon should carefully judge whether carotid intervention should be performed at all.

A key issue is that carotid revascularization must be done relatively quickly. The benefit of surgery fades quickly after 2 weeks have elapsed since the stroke event.\(^{43}\) Thus, the surgeon needs to be quick about triaging referrals and getting operative intervention organized and safely completed. Whether it is safe to operate early or later in this 2-week window remains unclear and is an urgent question to be resolved by a large-scale randomized clinical trial.\(^{44}\)

Stroke After Carotid Endarterectomy or Stenting

Stroke after carotid endarterectomy is fortunately uncommon. Over the course of two decades of CEA studies, the rate has fallen below 2%.\(^{45}\) Perioperative stroke is more common after carotid artery stenting.\(^{45}\) Mechanisms of stroke after CEA include thrombosis at the operative site with carotid occlusion, arteroembolism, or both. Prolonged clamp times in the setting of inadequate collateral circulation may result in stroke without obvious occlusion. Other mechanisms of stroke may coexist, such as atrial fibrillation, which can result in cardioembolic events occurring perioperatively.

A rapid clinical diagnosis and arterial diagnosis must be achieved. CT angiography is very helpful acutely. Reoperation with thrombus aspiration is a possible acute treatment. Endovascular intervention may be undertaken for distal arteroembolic occlusion. In the setting of partially occlusive thrombus at the site of the arteriotomy, we have found that intravenous bolus dosing of platelet antagonists such as abciximab is useful.\(^{46}\) It has been demonstrated that acute loading of clopidogrel reduces emboli detected by transcranial Doppler ultrasonography.\(^{47,48}\)

Direct Extracranial–Intracranial Bypass

Direct extracranial (EC) to intracranial (IC) vessel bypass is rarely used in acute stroke. It is reserved for unusual situations such as moyamoya syndrome.\(^{49}\) Rarely, young and otherwise healthy patients might have bilateral carotid dissections or other massive impairment of the proximal or intracranial circulation. Such patients may be candidates for direct EC–IC bypass to restore the circulation and prevent a slow, evolving infarction. Individualized patient selection, guided by imaging, is required to identify these uncommon patients. Decisions to proceed with this kind of intervention will never be guided by randomized controlled trials but instead by clinical evaluation, physiology, surgical expertise, and imaging.

Blunt Arterial Injury and Dissection in the Trauma Patient

The blunt trauma patient may have suffered enough force to the neck to result in blunt arterial injury. This is common in the vertebral arteries when there is a frac-
ture extending through the transverse foramen in the lateral process of the vertebrae, indicating substantial force application in this anatomic region. Carotid artery injuries may also occur, typically at the skull base. Although orthopedically stable, these injuries may result in stroke due to arteroembolism of an intraluminal thrombus at the site of injury. Sometimes there is a frank dissection of the artery; however, it is critical to label these injuries as blunt arterial injuries, with awareness that one subset of these is traumatic arterial dissection. Treatment is typically medical with antiplatelet (acetylsalicylic acid [ASA], clopidogrel) or antithrombotic medication (heparins). The prognosis is typically good; only a minority of patients will suffer a stroke.

Screening of trauma patients with CT angiography identifies many patients with asymptomatic dissection. Without pseudoaneurysm formation, these lesions tend to be benign and can be managed expectantly and conservatively just with ASA daily. Patients with an SAH associated with a dissecting pseudoaneurysm are at high risk of death. Management usually required sacrifice of the relevant artery.

Pharmacologic Treatment with Fibrinolytic and Antithrombotic Agents

Fibrinolytic Agents

In North America, tPA is the most used fibrinolytic agent for stroke both intravenously and endovascularly. Streptokinase trials were done early, and streptokinase was associated with an increased risk of intracerebral hemorrhage. Tenecteplase (TNK-tPA, TNKase) is under ongoing investigation for stroke and may replace tPA in the future.50–52 Desmoteplase is similarly under ongoing investigation for stroke.53 Urokinase is still available in some jurisdictions and has been used both intravenously and intra-arterially with success.

Antiplatelet Agents

Acetylsalicylic acid (ASA, aspirin) is the most commonly used antiplatelet agent. It inhibits cyclooxygenase-1 enzyme, reducing platelet aggregation. It is safe and inexpensive, and modestly beneficial in preventing stroke. Clopidogrel is a prodrug that is metabolized in the liver to an active thiol metabolite, which irreversibly inhibits the platelet P2Y12 adenosine diphosphate receptor, blocking platelet aggregation. Clopidogrel requires oral administration, and a loading dose is required to obtain adequately rapid platelet inhibition. The novel drugs ticagrelor and prasugrel, also P2Y12 adenosine diphosphate receptor inhibitors, have not been tested in stroke, but both are promising because they are available in intravenous formulation.

The combination of ASA and clopidogrel has been shown to reduce the chance of early recurrent stroke after initial TIA or minor stroke.54,55 Similarly, treatment with clopidogrel after CEA has been shown to reduce postoperative emboli detected by transcranial Doppler.47

The glycoprotein (GP)IIb/IIIa inhibitors abciximab and eptifibatide have been investigated in stroke. Abciximab was not associated with a better outcome in routine acute ischemic stroke treatment. Eptifibatide is being investigated in combi-
nation with low-dose tPA for the treatment of acute ischemic stroke. These drugs are used in the endovascular suite when patients suffer thrombotic complications of aneurysm coiling or other intra-arterial interventions. However, no studies that have convincingly demonstrated that this is an effective and safe approach to treatment. Experience suggests that intra-arterial administration of abciximab is associated with recanalization of occluded intracranial arteries after iatrogenic occlusion with aneurysm coiling. Tirofiban, a nonpeptide GPIIb/IIIa antagonist, reduces cerebral embolism from carotid artery plaque. Routinely, these drugs are not used in the treatment of stroke.

**Anticoagulants**

In general, both unfractionated and low molecular weight heparins are not beneficial in ischemic stroke. There is a small increase in the risk of major intracranial hemorrhage. Trials that have examined heparin use are now dated; patients with stroke enrolled in these trials were not differentiated with imaging. We reserve the use of heparins for situations where there is proven intravascular thrombus, limit its use, and use conservative approaches such that the partial thromboplastin time (PTT) or anti-Xa activity is not excessive at first dosing. The risk of major hemorrhage with unfractionated heparin is, in part, related to longer PTT times. In general, very few patients with ischemic stroke warrant treatment with full-dose heparins.

Pulmonary thromboembolism (DVT and PE) prophylaxis warrants the use of heparin. We used enoxaparin 40 mg once daily given subcutaneously based upon the PREVAIL study.

**Oral Anticoagulants and Reversal**

Oral anticoagulation using a vitamin K antagonist (coumarin) is the accepted standard for stroke prevention in atrial fibrillation and for other potential cardioembolic sources of stroke (e.g., prosthetic heart valve). Recently, novel oral anticoagulants have been introduced. These include dabigatran, a direct thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban, which are direct factor Xa inhibitors. Dabigatran, rivaroxaban, and apixaban are now approved in most jurisdictions for stroke prevention in atrial fibrillation. A similar path is expected for edoxaban.

For the neurosurgeon, a key issue with these medications is reversal when there is a need for urgent surgery. Vitamin K antagonists may be reversed with prothrombin complex concentrates (Octaplex™, Beriplex™) and vitamin K and fresh frozen plasma. Prothrombin complex concentrates work in minutes. Fresh frozen plasma takes hours to infuse and reestablish normal clotting parameters. Vitamin K restoration results in a normal international normalized ratio (INR) in 12 to 24 hours when the liver has normal synthetic function. Factor VIIa administration will normalize the INR, but it is less clear if clotting is truly normalized.

In contrast, there are no rapidly acting reversal agents for any of the novel anticoagulants. Because the half-life of these drugs is on the order of 8 to 12 hours, fully normal coagulation will not occur for 2 to 3 days with normal metabolism. Some blood products, including activated prothrombin complex concentrates (e.g., factor eight inhibitor bypass activity [FEIBA]) or activated factor VIIa combined with tranexamic acid have been suggested.
KEY POINTS

- Time is brain in most aspects of acute neurosurgical care of stroke. Care delayed is care denied.
- Decompressive hemicraniectomy and suboccipital craniectomy are lifesaving procedures that are ideally performed early in the course of stroke.
- Carotid revascularization is not a procedure that can wait. In good operative candidates, it should be performed within days of the symptomatic event.
- Carotid endarterectomy is the preferred procedure, over carotid artery stenting, for stroke prevention.
- The management of the acute ischemic stroke patient is a team affair. The vascular neurosurgeon should work closely with the stroke unit team to ensure effective and rapid care can be delivered.
- The vascular neurosurgeon plays a key role on the stroke team.
- Routine concerns such as carotid revascularization play a day-to-day role.
- Less commonly the surgeon has a critical role to play in managing severely affected patients with malignant MCA or PICA territory infarction.
- The surgeon-interventionalist may play a critical role in the endovascular management of acute ischemic stroke.

REVIEW QUESTIONS

1. Stroke is defined as a sudden vascular syndrome of the brain. Which is the most common stroke type?
   A. Intracerebral hemorrhage
   B. Transient ischemic attack
   C. Ischemic stroke
   D. Atraumatic subarachnoid hemorrhage
   E. Venous sinus thrombosis

2. Stroke is clinically defined by its presentation and is typically easy to diagnose. However, other conditions can mimic stroke. Common stroke mimics include which of the following?
   A. Migraine
   B. Seizure
   C. Subdural hemorrhage
   D. Hypoglycemia
   E. All of the above

3. The most important risk factor for stroke of all types is:
   A. Atrial fibrillation
   B. Diabetes mellitus
   C. Current cigarette smoking
   D. Hypertension
   E. Hyperlipidemia

4. Hemicraniectomy for malignant MCA infarction is a proven therapy. What have trials demonstrated?
   A. Hemicraniectomy should be performed more than 48 hours after stroke onset.
   B. Removal of brain tissue is warranted to prevent malignant swelling.
C. Patients over the age of 60 were included in the studies of hemicraniectomy.
D. The benefit of hemicraniectomy applies to both right and left hemisphere stroke.

5. Suboccipital craniectomy for massive swelling of a PICA territory inferior cerebellar infarction is a poorly studied intervention. What do we know about suboccipital craniectomy?
   A. It is probably a lifesaving intervention.
   B. It should be done early to prevent sudden rostral-caudal degeneration.
   C. It may be combined with cerebellectomy to ensure adequate decompression.
   D. All of the above

6. Traumatic artery injury is common after blunt trauma and may cause stroke. True or false:
   A. Blunt traumatic arterial injury may result in vessel occlusion.
   B. Dissection is one subset of blunt traumatic arterial injury.
   C. The mechanism of stroke may include vessel occlusion and arteroembolism.
   D. Asymptomatic blunt arterial injury may be managed with simple antiplatelet therapy alone.

References


**ANSWER KEY**

1. C
2. E
3. D
4. D
5. D
6. A: True; B: True; C: True; D: True
Manipulation of catheters, coils, balloons, and stents within the blood vessels makes the issue of coagulation most relevant to the endovascular neurosurgeon. The interventionalist must be constantly aware of the coagulation status of the patient to optimize patient management and to remain in neutral balance between the risk of thromboembolic and hemorrhagic complications. This, in turn, requires thorough knowledge of the mechanisms of platelet aggregation; of the numerous anti-thrombotic therapies available, including antiplatelet agents, anticoagulants, and fibrinolytic compounds; as well as the agents that reverse their effects.

This chapter reviews the basic issues and commonly used management paradigms used before, during, and after neuroendovascular procedures. Also addressed will be the coagulation issues related to specific techniques, including embolization, stenting, thrombolysis, as well as iatrogenic complications such as hemorrhage. Strategies for monitoring the coagulation status as well as the indications and methods of anticoagulation reversal postprocedure are also described here.

**Issues related to the Use of Anticoagulants Before and During Endovascular Procedures**

**General Neuroendovascular Procedures: Angiography, Aneurysm Coiling, Embolization of Arteriovenous Malformation or of Tumor**

The risk of thromboembolic complications associated with angiographic procedures makes the issue of anticoagulation particularly important. Diffusion-weighted imaging lesions after endovascular procedures have been reported to occur at rates as high as 69%, although most of these radiographic lesions are asymptomatic. Clinically evident permanent neurologic complications associated with diagnostic angiography are reported to occur in 0.5% of cases, and in 6 to 9% of neurointerventional procedures such as aneurysm coiling. The clinical incidence of stroke due to arteriovenous malformation (AVM) and tumor embolization is more likely related to the embolysate material penetrating blood vessels supplying normal tissue rather than to inadequate anticoagulation during the procedure.

For any angiographic procedure, it is generally desired that the prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time (PTT) be normalized prior to puncture of the femoral artery. For patients on a continuous infusion of intravenous (IV) heparin, this implies that the infusion be...
stopped for 1 to 2 hours and that the PT be checked prior to the procedure. These measures will help to prevent groin-site complications such as retroperitoneal hemorrhage that may result from repeated arterial punctures due to potentially difficult femoral access. An alternative approach to those patients on intravenous heparin who are particularly prothrombotic includes continuing their medication while the groin puncture is performed, but to be prepared for immediate reversal with protamine if arterial access becomes complicated.

For those patients on warfarin, it is recommended that their INR be reversed prior to puncture, because hemorrhage complicating femoral artery access could persist for several hours before obtaining reversal with appropriate blood products or vitamin K. If anticoagulation cannot be safely reversed and there is no significant urgency to the procedure, then the INR should be allowed to drift downward spontaneously before carrying out angiography, or the patient can be bridged with heparin. If the procedure is being performed on an anticoagulated patient with an acute hemorrhage or for an urgent or emergent indication, then the INR should be actively reversed with blood products such as fresh frozen plasma (FFP), cryoprecipitate, or vitamin K.

Dabigatran is an oral direct thrombin inhibitor that is an alternative treatment to warfarin used in the prevention of stroke in patients with nonvalvular atrial fibrillation. This medication should be discontinued 1 to 2 days prior to nonurgent endovascular procedures. However, in acute clinical scenarios that require urgent reversal of anticoagulation, there is no antidote or reversal agent currently available for dabigatran. Administration of FFP or prothrombin complex concentrate (PCC) may attenuate the anticoagulation effects of dabigatran and should be given as a last resort. Because dabigatran is cleared via renal pathways, hemodialysis is an option to accelerate the elimination of dabigatran but is not a practical option in most cases. A normal PTT value in a patient taking dabigatran suggests that little anticoagulation activity is present.

Endovascular catheters and wires exposed to blood flow serve as a nidus for thrombus formation. Catheters are generally made from polyurethane, polyvinylchloride, or polyethylene, whereas wires can be made from stainless steel, nitinol, or platinum. A hydrophilic coating made from polytetrafluoroethylene (Teflon) is typically, but not always, present on microcatheters and guidewires. Catheters and wires with hydrophilic coatings generally reduce thrombogenicity compared with the nonhydrophilic types, but this also depends on the contrast agent being used and how catheters and devices are maintained during the procedures. Nearly all contrast agents reduce platelet aggregation, but this effect is more pronounced with ionic contrast agents. Nonionic contrast agents such as ioxixanol and iopromide are thought to be more thrombogenic compared with ionic types. Aggressive cleaning of catheters and wires, continuous flushing of catheters with heparinized saline, preventing stasis of flow around tips of catheters, avoiding catheter-induced vasospasm, and systemic heparinization all help to reduce the chance of thrombus formation.

There is no consensus data on the use of intravenous heparinization during conventional angiographic procedures. Generally, if the procedure is short and uncomplicated, such as a diagnostic angiography, no intravenous heparinization is required. If the procedure evolves into one requiring catheter exchanges or requires a longer than normal amount of time (upward of 30 to 45 minutes), then intravenous heparinization should be considered at a dose of 70 to 100 units per kilogram, to an activated clotting time (ACT) goal of 250 to 300 seconds, or at least double the baseline value.
Alternatives to heparin exist for patients with documented heparin-induced thrombocytopenia including argatroban. Argatroban can be used in doses of 350 µg/kg bolus over 3 to 5 minutes or a continuous drip of 10 to 25 µg/kg/min. As with heparin, ACT values of 250 to 300 seconds should be targeted. Other alternatives include bivalirudin, lepirudin, and danaparoid.

For AVM or tumor embolization procedures that are anticipated to be short, one could consider not systemically heparinizing the patient, which may aid in the overall goal of thrombosis of the target vascular lesion. However, as a general rule, if catheter exchanges are anticipated, large-bore catheters (> 5 French) are to be used, or if the procedure is expected to be long, then systemic heparinization should be administered.

For ruptured intracranial aneurysms, we prefer to withhold anticoagulation until the first coil has been deployed within the aneurysm dome. At that point, we proceed with a full dose of intravenous heparin. However, the protocol for anticoagulation treatment in patients with ruptured aneurysms is controversial and some interventionists prefer to systemically heparinize the patient prior to any embolization, whereas others prefer to heparinize after the aneurysm has been well coiled.

### Stents

Stenting procedures demand particular attention to the coagulation status of a patient because of the intent to introduce a therapeutic, but thrombogenic, foreign body permanently into the vascular system. Most of the experience with antiplatelet therapy in the setting of stent placement comes from cardiac procedures. Compared with coronary stents, however, intracranial stents are likely to be less thrombogenic because current versions used for carotid or intracranial atherosclerotic disease and aneurysm neck remodeling are self-expanding as opposed to the coronary balloon-expandable types. Self-expandable stents cause less mechanical stress to the underlying arterial surface, limiting the extent of endothelial injury and resulting in less thrombogenicity. Nevertheless, rates of thromboembolic complications with stent-assisted neuroendovascular procedures remain significant. The literature has reported stent-associated thromboembolic complication rates as high as 28%.

In elective cases likely to involve the placement of a stent, such as for carotid or intracranial atherosclerotic disease or for aneurysm neck remodeling, an antiplatelet regimen must be initiated before the procedure. Acetylsalicylic acid (ASA) 325 mg daily and a 2-day loading dose of clopidogrel 300 mg daily, followed by 75 mg daily, both beginning at least 2 days prior to and including the morning of the procedure, is recommended. However, if a stent is required more urgently, a loading dose of ASA 650 mg and clopidogrel 600 mg can be administered the day prior to the procedure followed by ASA 325 mg and clopidogrel 75 mg on the morning of the procedure. Ideally, platelet inhibition should be confirmed before the procedure because up to 65% of patients are resistant to conventional doses of ASA and up to 30% of patients are resistant to clopidogrel.

During the stenting procedure, intravenous heparinization should be performed to an ACT goal of 250 to 300 seconds, although some recommend reaching an ACT of 300 to 350 seconds because of the higher thromboembolic risk associated with these interventions. Following the placement of a stent, dual antiplatelet therapy with ASA 325 mg and clopidogrel 75 mg is recommended for a 6-week to 3-month
period, followed by ASA 325 mg indefinitely thereafter. In the case of drug-eluting stents, such as those occasionally placed for large-vessel extracranial disease, a longer duration of dual antiplatelet therapy, typically 6 months to 1 year, is required because of the prolonged period necessary for endothelialization.

Stent placement is generally not recommended in the setting of acute intracranial hemorrhage. Nevertheless, situations may arise that demand deployment of a stent in a patient with acute bleeding, such as in the case of proximal atherosclerotic disease limiting endovascular access to a more distal target, arterial hemorrhagic dissection, or coil herniation from a ruptured intracranial aneurysm. In these situations, a stent may be necessary, leaving the interventionist to propose an antiplatelet regimen that prevents stent-associated thrombosis and thromboembolism while minimizing the risk of further hemorrhage.

If a stent is required in the setting of an acute intracranial hemorrhage, the glycoprotein (GP)IIb/IIIa inhibitor abciximab can be administered intra-arterially and locally at the site of recent stent deployment through the microcatheter. However, this should be done only after securing the culprit vascular lesion, such as a ruptured aneurysm. A bolus dose of 0.1 to 0.25 mg/kg is generally given, or a dose titrated to a GPIIb/IIIa receptor inhibition level of 50%. Immediately following the procedure, and after ensuring no hemorrhage at the arterial access site, a loading dose of ASA 325 to 650 mg and clopidogrel 300 mg daily for 2 days and then 75 mg thereafter should be implemented for dual antiplatelet therapy as described previously.

Acute Stroke

Stroke patients present several important challenges for the neurointerventionist. Many of these patients have preexisting vascular disease, are already on one or more antiplatelet medications, and, in addition, will have received intravenous tissue plasminogen activator (tPA) if they present within the 4.5-hour time window from the onset of symptoms. Furthermore, potential hemorrhagic conversion of the infarcted territory or reperfusion hemorrhage after successful revascularization are serious considerations that affect the choice of anticoagulation in these patients.

If IV tPA has recently been administered, and the patient becomes a candidate for an attempt at endovascular revascularization, it is reasonable to proceed without further anticoagulation. It is in general advisable not to administer antiplatelet or anticoagulant medications within 24 hours of treatment of IV tPA. It must be kept in mind, however, that tPA has a relatively short half-life (2 to 12 minutes) and that recommended time windows for endovascular revascularization are as long as 8 hours for anterior circulation strokes and up to 12 hours for basilar artery occlusions. Hence, if endovascular revascularization is attempted more than 1 to 2 hours after intravenous tPA administration or if none was given, then intravenous heparinization should be given soon after femoral access has been established to prevent the additional risk of thrombus formation associated with intra-arterial catheter manipulation as well as with endothelial injury from the various reperfusion methods available. If intravenous heparin is administered for attempted endovascular thrombolysis after intravenous tPA has been given, a postprocedure noncontrast computed tomography (CT) scan should be considered after the procedure to rule out any intracranial hemorrhage.

The specific revascularization strategy used for arterial stroke depends on the experience of the interventionist, and characteristics of the lesion itself. Intra-
arterial thrombolysis has the theoretical advantage of higher doses of agent being directed at the target site, with lower systemic exposure. Currently, the only thrombolytic agent approved for intra-arterial use is tPA, although other non-thrombolytic agents such as GPIIb/IIIa inhibitors are being used at some centers. Intra-arterial tPA can be used as a therapeutic adjunct to IV tPA in patients who present within 6 hours of symptoms onset, and its use has been supported by several trials including the Emergency Management of Stroke (EMS) trial as well as the Interventional Management of Stroke (IMS-I) trial. According to the IMS-I trial, the microcatheter is first positioned beyond the thrombus and 2 mg of tPA is injected over a 2-minute period. The catheter is then retracted into the thrombus, and 2 mg of tPA is injected directly into the thrombus over another 2-minute period. Continuous infusion of tPA is then started at a rate of 9 mg/h for up to 2 hours or until thrombolysis is achieved. An ongoing IMS-III trial will further help to evaluate the effectiveness of combined IA and IV tPA therapy compared with IV tPA alone.

Several device options for arterial stroke revascularization are available, including simple mechanical clot disruption (with microcatheter or microwire), thrombus retrieval devices (Merci retriever, Concentric Medical, Mountain View, CA), stent-based retrieval devices (Solitaire, ev3 Endovascular Inc., Plymouth, MN; Trevo, Stryker, Morrisville, PA), mechanical and vacuum thrombolysis (Penumbra, Penumbra Inc., Alameda, CA), or venturi-based thrombectomy (AngioJet, Medrad Inc., Warrendale, PA). In many cases, these devices are being used as first-line therapies, with or without the addition of intra-arterial tPA. Tissue plasminogen activator (tPA) as an adjunctive treatment includes those occasions in which revascularization with the device methods reveals distal emboli (present since the onset of the symptomatic occlusion, or inadvertently caused iatrogenically during endovascular manipulations resulting in portions of thrombus migrating distally). In some instances, tPA is being used after failed mechanical revascularization. The intra-arterial dose of tPA used in these settings is typically administered in 1- to 3-mg aliquots with intermittent angiography to see if the desired effect has been achieved.

Cases of Venous Thrombosis

Endovascular treatment of dural sinus or deep cerebral vein thrombosis is increasingly common. The issues surrounding anticoagulation treatment for venous thrombosis are especially complex due to the propensity for hemorrhagic conversion of venous infarcts. Patients with venous thrombosis and without a significant intracerebral hemorrhage should be placed on intravenous heparin as soon as the diagnosis has been made. In patients being treated with intravenous heparin, whether or not to stop the heparin infusion prior to obtaining groin access is practitioner-dependent. If possible, access should be limited to the venous system, to avoid the added complexity of a potential arterial groin site complication in the setting of full heparinization.

As for arterial cases, several options for endovascular venous thrombolysis are available. These include simple mechanical clot disruption (with microcatheter or microwire), mechanical and vacuum thrombolysis (Penumbra), as well venturi-based thrombectomy (AngioJet). Restoration of at least some flow through the thrombosed venous channel is the goal, because this seems to predict persistent patency of the thrombosed venous segment. Instillation of tPA within the clot is
often performed as with arterial thrombolysis cases. In our experience, however, venous heparin should be administered continuously during the procedure as well as during the immediate postoperative period, and patients should subsequently be bridged to oral anticoagulation with warfarin once stabilized.

Another option for patients with venous thrombosis is locally administered tPA within the thrombus, followed by a continuous intrathrombus infusion of tPA with simultaneous intravenous heparin. According to this protocol, 1-mg boluses of tPA are first instilled at 1- to 2-cm intervals of the thrombosis, and then the microcatheter is repositioned just proximal to the rostral end of the thrombus and intravenous tPA is administered through the microcatheter over a period of 12 to 24 hours.9 Patients are treated with concomitant intravenous heparin at twice the control levels of PTT. After 12 to 24 hours of continuous treatment, patients are reimaged with contrast venography and are subsequently bridged to oral warfarin therapy.

**Intraprocedural Thrombus**

Despite attempts to prevent thrombus formation during endovascular procedures, including aggressive catheter and wire maintenance, continuous flushing of catheters with heparinized saline, avoiding catheter-induced spasm, pretreatment with antiplatelets for stenting procedures, and adequate systemic anticoagulation, thromboembolic complications are not uncommon. For the interventionist, it is important to remain vigilant in the interpretation of the angiographic images so that early thrombus formation does not go unrecognized and early treatment for the thrombus can be implemented.

The most common locations for thrombus formation are at the tip of a guide catheter, within a stent, or adjacent to a coil mass. In one series, thrombus was identified at the coil–parent artery interface in 4.3% of cases.10 Heparinized saline drips should be monitored frequently and blood flow beyond the tips of guide catheters should be checked intermittently to look for thrombus as well as spasm induced by rubbing of the catheter tip against the vessel wall. Low magnification angiograms of the entire territory supplied by the vessels being manipulated should be performed pre- and postprocedure, and should be scrutinized for occlusions or sluggish flow. Close attention should also be paid to changes in electrophysiological monitoring, such as somatosensory evoked potentials (SSEPs) and electroencephalography (EEG) in patients who are under general anesthesia and the clinical exam in patients who are awake because, occasionally, these may be the first signs of a thromboembolic complication.

Platinum-based coils used for typical aneurysm embolization procedures are designed to promote thrombus formation at their site of deployment. They accomplish this primarily by the mechanism of electrothrombosis, in which the non-dissolvable positive charged end of platinum attracts negatively charged blood constituents including red blood cells, platelets, and fibrinogen.5 Coils with various surface coatings have been developed to further invoke the thrombogenic response, such as those coated with the polymers polyglycolide and polylactide (Axium, ev3; Matrix, Siemens Healthcare, New York, NY). Coils that are closely adjacent to or herniating out of the neck of the aneurysm, therefore, may produce thrombus that can embolize distally. During an elective aneurysm coiling, if a misplaced coil can-
not be retrieved, consideration can be given to placement of a stent to force the coil along the wall of the blood vessel. In either ruptured or unruptured cases, assuming the aneurysm is protected, the patient can be placed on ASA with or without clopidogrel to prevent a thromboembolic complication. The hemorrhagic risk of starting antiplatelet agents in a patient with subarachnoid hemorrhage after aneurysm occlusion is relatively low in our experience.

If thrombus is identified angiographically, the goal of management is to prevent progression to a clinically significant event. If there is complete occlusion of a vessel, the first steps in management include ensuring adequate hydration and raising the blood pressure. Intra-arterial tPA may be administered for a thrombolytic effect. The risk of a hemorrhagic event when tPA is used in the setting of an acutely ruptured aneurysm, however, is significant and should be avoided. Nonocclusive thrombus within a stent or associated with coils herniating into the parent vessel can be managed with antiplatelet agents, because they tend to be platelet-rich. To prevent recruitment of additional platelets and propagation of the thrombus, abciximab can be administered at a bolus dose of 0.1 to 0.25 mg/kg intra-arterially (in 2- to 5-mg aliquots) through a microcatheter positioned proximal to the thrombus. Alternatively, the entire calculated dose based on ideal body weight may be quickly given intravenously as a bolus to speed delivery. After groin hemostasis is achieved, the patient can be started on ASA with or without clopidogrel.

Strategies for Monitoring; Reversal of Anticoagulants/Antiplatelet Agents

Prior to procedures requiring the use of antiplatelet agents, such as elective stent placement, patients should be started on ASA and clopidogrel. Ideally, sensitivity to ASA and clopidogrel should also be verified prior to the procedure. Confirmation of platelet dysfunction can be done using either bleeding time or optical aggregometry. Alternatively, a point-of-care platelet function assay can be used, which is a bench-top unit using citrated whole blood and disposable test cartridges. ASA and clopidogrel resistance can be measured by assessing the response of platelets to the agonist adenosine diphosphate (ADP). Resistance to GPIIb/IIIa antagonists can be measured by the response of platelets to ADP as well as to other agonists such as thrombin receptor agonist peptides.

During the procedure, monitoring of ongoing intravenous heparinization is accomplished by means of the ACT. For most endovascular procedures, the ACT should be kept at 250 to 300 seconds, or at least double the baseline value. The ACT is determined by a bench-top analyzer that uses a mechanical clot detection mechanism. In this assay, whole blood is exposed to an activator of coagulation. A magnet is displaced once clot formation occurs, activating the alarm, and an ACT is reported. Typically, the first ACT is drawn 5 minutes after heparinization. Levels should be repeated every 30 to 45 minutes and again after completion of the procedure.

Upon completion of the endovascular procedure performed with full heparinization, the interventionist has the option of reversing anticoagulation. Pharmacological reversal can be performed with protamine at 1 to 1.5 mg for every 100 U of heparin given. We recommend checking the ACT at the end of the procedure and prior to removal of the access sheath, because if the ACT has already drifted into the normal range in an uncomplicated case, then pharmacological reversal may
not be required. In a case that is uncomplicated but with the propensity for hemorrhage in the early postoperative period, reversal prior to arterial sheath removal is suggested. In a case complicated by a hemorrhagic event, however, early and rapid reversal of anticoagulation should be instituted.

For procedures in which the risk of a thromboembolic complication is present primarily during the procedure itself, such as AVM, arteriovenous fistula (AVF), or tumor embolizations, reversal of anticoagulation prior to removal of the arterial sheath should be considered. Alternatively, the PTT can be checked 6 hours after procedure and, if normalized, the sheath can be removed at that time. Delayed removal, however, can lead to clot formation within or on the sheath, or femoral arterial dissection from excessive movement of the leg.

For patients with recent arterial stroke in whom tPA was not administered, it is reasonable to continue intravenous heparin in the postoperative period. Arterial sheath removal for these patients can be performed on a delayed basis 12 to 24 hours after the procedure, by first stopping the intravenous heparin for 2 hours and confirming a normal PTT prior to removal. Intravenous heparin may be resumed after hemostasis at the access site is ensured. Similarly, venous thromboembolism patients should be continued on intravenous heparin because reocclusion rates in these patients are high. After the thrombolysis procedure, the PTT should be maintained at therapeutic levels after the procedure with intravenous heparin, with or without a continuous microcatheter infusion of intravenous tPA at the site of thrombosis as previously described. A follow-up venogram is often performed the following day and, if the cerebral venous system has remained patent, the intravenous heparin can be temporarily stopped, the sheath removed, and heparin resumed. Subsequently, the patient can be bridged to oral anticoagulation with warfarin.

If a procedure is complicated by intracranial hemorrhage, such as an aneurysm perforation, the anticoagulation should be immediately reversed with protamine. Other measures used to prevent additional bleeding include lowering the blood pressure, expeditiously coiling the aneurysm, and balloon inflation across the aneurysm neck within the parent vessel. Evidence of hemorrhage at the femoral access site, such as constant oozing, a visibly enlarging hematoma, drop in hematocrit, or unexplained hypotension should be reason to reverse the anticoagulation, and an immediate CT scan of the abdomen/pelvis should be obtained.

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**Role for Anticoagulants/Antiplatelet Agents Postembolization**

In several instances, there is a role for continued treatment with anticoagulants or antiplatelet agents following embolization. These include procedures entailing thromboembolic complications, stroke (of arterial and venous etiologies), and after placement of a carotid or intracranial stent.

For thromboembolic complications, there is no evidence to guide the specific management and duration for antiplatelet therapies. If the thromboembolic event occurred secondary to a permanent and thrombogenic foreign body, then the ASA should be started after the procedure and continued indefinitely. It is recom-
mended, however, to obtain a noncontrast CT after the procedure to rule out a hemorrhagic complication prior to beginning antiplatelet therapy. Clopidogrel may be used in addition to ASA, especially if the patient experiences symptoms from the thrombus, and consideration can be given to discontinuing the clopidogrel after 4 to 6 weeks in the patient without recurrent symptoms. For thromboembolic events that occur in the setting of a subarachnoid hemorrhage and after the aneurysm has been secured, the risk of antiplatelet therapy is low. If thromboembolism occurred secondary to a transient cause such as that related to the guide catheter, then antiplatelet therapy can be instituted for a temporary period (2 to 4 weeks).

For secondary prevention in patients with noncardioembolic stroke or TIA, current recommendations are for oral antiplatelet regimens as opposed to oral anticoagulation. ASA and dipyridamole in combination are recommended over ASA therapy alone. Alternatively, clopidogrel monotherapy may be used. The combination of ASA and clopidogrel, however, is not routinely recommended due to the risk of hemorrhage unless, however, there is a specific indication for both medications such as after placement of a carotid or intracranial stent. For patients with cardioembolic stroke or TIA due to atrial fibrillation, oral anticoagulation with warfarin to a target INR between 2.0 and 3.0 is recommended. Dabigatran, a direct thrombin inhibitor, is an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with nonvalvular atrial fibrillation. The timing for initiation of anticoagulation in stroke patients is debated. In general, anticoagulation should be started within 2 weeks of an ischemic stroke. For patients unable to take warfarin, ASA 325 mg daily is recommended.

As described previously, following stent placement dual antiplatelet therapy with ASA 325 mg and clopidogrel 75 mg is recommended for 6 weeks to 3 months, followed by ASA 325 mg indefinitely thereafter. In the case of drug-eluting stents, such as those occasionally placed for large-vessel extracranial disease, a 6-month to 1-year course of dual antiplatelet therapy is required because of the longer period required for endothelialization. Stents typically used for aneurysm neck remodeling are only rarely associated with delayed in-stent restenosis, unlike those placed for atherosclerotic disease. Nevertheless, nearly all stents produce considerable artifact on CT and magnetic resonance imaging (MRI), so follow-up conventional angiography may be considered 6 weeks to 3 months postprocedure to reassess the original lesion, search for in-stent restenosis, and determine subsequent antiplatelet management.

**Conclusion**

Issues related to anticoagulation are particularly relevant to neuroendovascular procedures, in which both thromboembolic and hemorrhagic complications can occur. The interventionist can use several medications and maneuvers to help minimize risk of a thromboembolic or hemorrhagic event, as well as to reduce the chance of a poor clinical outcome if thrombus or hemorrhage is identified intra- or postprocedurally. Chapter 22 describes several specific case examples as they relate to bleeding and coagulation during neuroendovascular procedures.
KEY POINTS

- Intravascular manipulations are associated with the risk of thromboembolic complications.
- Intravenous systemic heparin should generally be administered for all endovascular interventional procedures.
- Intraprocedural thromboembolic complications should be managed with thrombolytic or antiplatelet agents.
- Intra- or postprocedural hemorrhagic events require immediate reversal of anticoagulation.

REVIEW QUESTIONS

1. Dabigatran, an oral thrombin inhibitor, is being used for anticoagulation in a patient with atrial fibrillation who suffers from a spontaneous intracerebral hemorrhage that has enlarged on serial scans. What is the most appropriate therapy?
   A. Administration of fresh frozen plasma (FFP) or prothrombin complex; consider hemodialysis.
   B. Expectant management
   C. Infuse platelets
   D. Infuse protamine sulfate

2. The primary mechanism for thrombus formation within an aneurysm embolized with a platinum coil is:
   A. Electrothrombosis
   B. Endothelial damage
   C. Factor VII activation
   D. Release of tissue factor

3. During coil embolization of an unruptured carotid artery aneurysm, a postembolization angiogram demonstrates partial occlusion of a distal left MCA branch on the same side. What is the most appropriate therapy?
   A. Antiplatelet therapy in combination with Coumadin
   B. ASA administration
   C. Intra-arterial abciximab infusion followed by antiplatelet therapy
   D. No treatment

4. The most common complication associated with deploying an intracranial arterial stent is:
   A. Acute vessel occlusion
   B. Arterial dissection
   C. Thromboembolic complications
   D. Femoral artery bleeding

5. A patient has an intra-arterial stent placed for flow diversion treatment of an intracranial aneurysm. What is the subsequent recommended antiplatelet or anticoagulation therapy?
   A. ASA 81 mg daily for 6 weeks to 3 months
   B. ASA 325 mg daily for life
C. Clopidogrel 75 mg and ASA 325 mg daily for 6 weeks to 3 months, followed by ASA indefinitely
D. Therapeutic warfarin

References


ANSWER KEY

1. A
2. A
3. C
4. C
5. C
Neuroendovascular-Specific Patient/Case Examples

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Anticoagulation management is an important aspect of endovascular neurosurgical interventions. This chapter presents specific cases to highlight the anticoagulation regimen employed. For each case, a short discussion explains the course of action and suggests other reasonable management options for similar circumstances.

Arteriovenous Malformation

History

A 40-year-old woman presented with a new onset of seizure. Clinically, she was neurologically intact. Computed tomographic (CT) scan showed a right frontal intraparenchymal hemorrhage, and CT angiography demonstrated abnormal vessels consistent with a Spetzler-Martin grade 2 arteriovenous malformation (AVM) (Fig. 22.1). Given her age, good clinical examination, ruptured status, and accessible location of the AVM, a preoperative embolization followed by surgical resection was planned.

Procedure

The procedure was performed under general anesthesia 2 days after her presentation. Systemic heparinization was not performed, given her recent hemorrhage. After femoral access was obtained, angiography was performed that demonstrated the AVM to be fed by the medial orbitofrontal and frontopolar branches of the anterior cerebral artery (Fig. 22.1b,c). Embolization of the lesion was performed using 1:3 mixture of N-butyl cyanoacrylate (NBCA) glue and Ethiodol, without complication (Fig. 22.1d). Surgical resection was planned for the following day, and the patient was left intubated in the interim because of a difficult airway. Because an intraoperative angiogram was anticipated, the femoral sheath was left in place with a 1:1 mixture of heparinized saline solution (500 cc normal saline with 500 units of heparin) infusing at 15 cc/hour overnight.

The patient underwent surgical resection the following day, with intraoperative angiography demonstrating no residual lesion. The sheath was removed in the intensive care unit postoperatively by applying manual pressure for 15 minutes. The patient was left intubated for blood pressure control overnight and was extubated the next day. She remained neurologically intact.
No systemic heparinization was performed during this procedure because of her recent intracranial hemorrhage due to AVM rupture. If surgical resection with intraoperative angiography is planned for the following day, the option of leaving the sheath in place is a reasonable one, especially if the patient is to remain intubated. This avoids the patient having to undergo multiple femoral punctures each with a risk of groin complications. However, if the patient is extubated between the embolization and surgical procedures, excessive leg movement with the sheath in place may also lead to complications such as arterial dissection. If the sheath is left in place, femoral thromboembolic complications can be avoided by an infusion of heparinized saline solution.

**Fig. 22.1a–d**  (a) Axial computed tomography (CT) demonstrating right frontal intraparenchymal hemorrhage. (b) Early- and (c) late-phase lateral projection angiogram of the right internal carotid artery (ICA) demonstrating the Spetzler-Martin grade 2 arteriovenous malformation (AVM). (d) Postembolization angiography demonstrating absence of early venous drainage.
Aneurysms: Case 1

History

A 73-year-old woman, a smoker with a history of migraine headaches, experienced the sudden onset of retro-orbital pain behind her left eye. She did not seek medical care initially, even though the usual treatments for her migraines did not relieve her symptoms. About 10 days later she developed difficulty speaking, after which she presented to her physician. Clinically, she was neurologically intact with the exception of moderate expressive dysphasia. Imaging included a magnetic resonance (MR) angiogram that demonstrated a 6-mm left-sided superior hypophyseal aneurysm, and a right-sided 4-mm superior hypophyseal aneurysm. Magnetic resonance fluid-attenuated inversion recovery (FLAIR) imaging showed leptomeningeal signal in the left sylvian fissure, suggestive of past hemorrhage, and diffusion-weighted imaging demonstrated several subacute strokes in the left middle cerebral artery (MCA) territory.

Procedure

The patient underwent urgent coil embolization of the left superior hypophyseal aneurysm, due to presumed rupture. One month later, she was readmitted electively for planned coil embolization of her right superior hypophyseal aneurysm. Systemic anticoagulation was administered with 70 U/kg of intravenous heparin after groin access was obtained. After initial angiography, it was felt that a stent would be required to successfully coil the wide-necked aneurysm (Fig. 22.2a). The stent was deployed successfully.

Then attention was turned to advancing the microcatheter into the aneurysm. The acute angle between the aneurysm and the parent vessel of the aneurysm made it technically difficult to direct the microcatheter directly into the aneurysm. For this reason, the decision was made to advance a balloon para-axially to assist with keeping the microcatheter directed into the aneurysm. After the balloon was maneuvered into the region of the aneurysm, an angiogram through the guide catheter was performed. It demonstrated a filling defect within the stent and within the posterior communicating artery consistent with acute thrombus formation (Fig. 22.2b).

The balloon was immediately removed from the patient. A total of 8 mg of abciximab was injected through the microcatheter, with its tip sitting just proximal to the stent. Angiography through the guide catheter was then performed demonstrating some, but not complete, resolution of the thrombus within the stent, and improved flow through the posterior communicating artery (Fig. 22.2c).

Given the difficulty in catheterizing the aneurysm and the subsequent thrombus formation, the attempted coiling procedure was aborted. The patient was allowed to awaken from general anesthesia and was loaded on acetylsalicylic acid (ASA) 325 mg and clopidogrel 300 mg 4 hours after groin closure. Her immediate postoperative course was uncomplicated and she was discharged the following day. One month later, she underwent uncomplicated balloon-assisted coiling of the right superior hypophyseal aneurysm through the previously placed stent.
Discussion

There are several important points to learn from this case. Based on clinical history, there is suspicion that the patient’s headache represented an aneurysmal subarachnoid hemorrhage. Her difficulty speaking and her strokes were likely caused by vasospasm secondary to the hemorrhage. Despite this, systemic heparinization was performed soon after groin access was obtained, because the risk of rehemorrhage from anticoagulation was thought to be low. In comparison, acute subarachnoid hemorrhage patients who undergo coiling procedures are typically not heparinized until after the first coil is placed, although there is some variation in this practice.

The placement of a stent for the patient’s wide-necked aneurysm was not anticipated. Therefore, premedication with ASA and clopidogrel was not prescribed before the second procedure, which would have reduced the chance of a thromboembolic complication. Furthermore, technical factors including the acute angle between the aneurysm and the parent vessel increased the length of time required for the procedure.

The delay between placement of the stent and administration of the antiplatelet agent abciximab, and the use of a balloon as an additional adjunctive device also contributed to thrombus formation. When thrombus is observed, it is import-
ant to immediately remove devices that are contributing to its formation and that are no longer required, such as the balloon in this case.

After administering abciximab, it was important to abort the attempted coiling procedure, as was done in this case. Further attempts at coiling can disrupt the thrombus and cause it to migrate distally, resulting in a stroke. Also, because the unruptured aneurysm had not yet been treated, the risk of a major hemorrhage with inadvertent aneurysmal perforation after administration of abciximab would be significant. Aborting the procedure and awaking the patient also allows for an examination to assess for any neurologic injury. Because thrombus formation required the catheters to be pulled proximal to the stent, aborting the procedure also enables integration and endothelialization of the stent before a reattempt at coil embolization, in this case occurring 4 weeks later.

Aneurysms: Case 2

History

A 46-year-old healthy, non-smoking, right-hand-dominant man from a rural town suffered a sudden-onset headache associated with nausea, vomiting, photophobia, and neck stiffness. He was seen at a local hospital, and a CT scan revealed thick subarachnoid blood in the basal cisterns and in the anterior interhemispheric fissure with no evidence of hydrocephalus. CT angiogram revealed a 6-mm bilobed anterior communicating artery aneurysm directed anteriorly with a relatively narrow neck. He received a 1000-mg intravenous dose of tranexamic acid and was urgently transferred via air ambulance to a tertiary care center with neurosurgical services. Clinically, he was neurologically intact.

Procedure

The patient proceeded to undergo urgent unassisted endovascular coiling of the ruptured anterior communicating artery aneurysm under general anesthesia. The diagnostic angiogram via the right internal carotid artery (ICA) confirmed the presence of the aneurysm arising from the right A1/A2 junction with good cross-filling into the left anterior cerebral artery (ACA) and middle cerebral artery (MCA) branches through the anterior communicating artery (Fig. 22.3a).

A microcatheter was advanced into the aneurysmal sac. Prior to insertion of the first coil, however, there was a small-volume rupture confirmed with injection via the guide catheter. This resolved spontaneously without any hemodynamic changes. After the first coil was deployed, the patient received systemic anticoagulation with 70 U/kg of intravenous heparin (Fig. 22.3b). A second coil was then deployed, after which there was a second, larger intraprocedural rupture (Fig. 22.3c). This was associated with hypertension (190/100 mm Hg) and bradycardia (heart rate of 40). In response, protamine was immediately administered by the anesthetist to reverse the heparin. Given that more than 30 minutes had elapsed since the initial administration of heparin, 5 mg of protamine for every 1000 units of heparin was given, and additional coils were placed to protect the fundus of the aneurysm.

A right frontal external ventricular drain (EVD) was placed on an emergent basis in the angiography suite. An angiogram performed 3 minutes after the second rup-
The patient was very slow to wake from the general anesthesia but remained neurologically intact. The patient was weaned off the EVD and it was removed 7 days later. The patient had an uneventful hospital stay and was discharged neurologically intact 2 weeks after admission.

Discussion

There are several points to learn from this case of intraprocedural rupture in a patient with aneurysmal subarachnoid hemorrhage. Given that the patient resided far from a center with neurosurgical expertise (> 500 km), tranexamic acid was prescribed over the phone to prevent rebleeding prior to transport. Tranexamic acid is an antifibrinolytic that is known to decrease the rebleeding rate in patients with ruptured intracranial aneurysms. However, the use of antifibrinolytics does not improve overall clinical outcomes, likely due to the increase risk of cerebral ischemia. Use of tranexamic acid prior to aneurysm treatment should not be routine, but may be useful when there is likely to be a delay in securing the aneurysm because of a long travel time.
During the endovascular procedure, this patient had two intraoperative ruptures, but only the second larger rupture produced hemodynamic changes. When an intraprocedural rupture occurs, there is a sudden increase in the intracranial pressure that may produce a Cushing response (hypertension, bradycardia) as well as pupillary dilatation. The immediate response should be to reverse any anticoagulation that has already been administered. As a general guideline, if less than 30 minutes has elapsed since heparin administration, then 10 mg of protamine for every 1000 units of heparin should be given. If more than 30 minutes has elapsed, then the protamine dose should be halved. The blood pressure should be reduced acutely. The aneurysm should be packed quickly with additional coils with the goal of occluding the fundus of the aneurysm. Clear communication between the neurointerventionist and the anesthetist is critical.

Placement of an EVD should be strongly considered in the setting of intraprocedural rupture, especially when hemodynamic changes are present. This should be done on an emergent basis but only after protamine has been administered to reverse the heparin, given the risk of causing an iatrogenic intracerebral hematoma.

Carotid Artery Stenting

History

A 41-year-old otherwise healthy man was riding his bicycle and had an accident in which he was thrown from his bicycle. There was no loss of consciousness. Several hours later, he experienced sudden onset of expressive and receptive speech difficulty as well as right-sided weakness. This episode was witnessed by his wife, who noted a second similar episode on their way to the emergency department. He was neurologically intact on exam. Magnetic resonance imaging (MRI) demonstrated an area of restricted diffusion in the left insula, and MR angiography revealed a flow-limiting left ICA dissection and pseudoaneurysm of the distal cervical and proximal petrous segments. He was immediately given ASA 325 mg and daily thereafter, and was booked for urgent endovascular intervention of his left ICA dissection.

Procedure

The procedure was performed under general anesthesia 2 days after his presentation. After femoral access was obtained, heparin was administered at a dose of 70 U/kg. A guide catheter was subsequently navigated into the left common carotid artery and angiography confirmed the MR angiography findings (Fig. 22.4a). Stenting of the pseudoaneurysm was performed without complication, followed by balloon angioplasty (Fig. 22.4b). A post-stenting and angioplasty angiographic image of the stented segment and the left ICA branches demonstrated a good result without obvious thromboembolic complications. Abciximab 5 mg was then administered prophylactically through a microcatheter placed just proximal to the stent.

Following the procedure, femoral artery closure was obtained using a closure device. Because systemic heparinization as well as abciximab were administered during the procedure, the femoral puncture site was clamped for an additional 10 minutes to prevent bleeding. The patient tolerated the procedure well and awoke
neurologically intact. An additional ASA 325 mg and clopidogrel 300 mg were administered 6 hours after the procedure after ensuring hemostasis at the femoral access site. Clopidogrel 300 mg was also administered the following day and at a dose of 75 mg daily thereafter.

Angiography performed 3 months later demonstrated remodeling of the dissected segment and excellent patency of the vessel through the stented segment (Fig. 22.4c). The clopidogrel was discontinued at that time while ASA was continued at the same dose.

Discussion

Acetylsalicylic acid was administered early in this case due to the positive diffusion-weighted imaging and the possibility of embolic infarction resulting from the ICA dissection. It was elected not to administer clopidogrel preprocedurally because of the history of recent trauma. In the case of spontaneous dissection without evidence
of trauma or hemorrhage, it may be reasonable to administer both ASA and clopi-
dogrel preprocedurally up to and including the day of the endovascular procedure
to minimize the risk of thromboembolic complications.

Immediately after stent placement, it is important to obtain an angiogram of
the branches distal to the stented vessel to rule out thromboembolic events. This
is especially important for cases in which pretreatment with ASA and clopidogrel
is not performed. A final angiogram following abciximab administration should be
scrutinized for any extravasation of contrast.

After placement of a stent, both ASA and clopidogrel should be taken for 6
weeks to 3 months. In the case of drug-eluting stents, the time frame is typically
6 months to 1 year due to delayed endothelialization. Follow-up imaging should be
acquired at corresponding time points and, if no in-stent restenosis is identified,
the clopidogrel can be stopped while ASA should be continued indefinitely.

**Stroke: Mechanical Thrombectomy with a Retrievable Stent**

**History**

A 60-year-old right-hand-dominant man with a medical history of hypertension
experienced a sudden onset left-sided weakness and neglect. He was seen in the
emergency department 1 hour after onset of neurologic symptoms. Neurologic
exam revealed left upper extremity flaccid plegia, and left lower extremity paresis
but with partial antigravity strength. He had a left lower facial droop and bilateral
cerebral ptosis. His eyes were deviated to the right and he had profound left-sided
neglect. He was able to follow simple commands but had limited verbal output. His
baseline National Institutes of Health Stroke Scale (NIHSS) score was 18.

Urgent noncontrast CT scan of the head revealed a hyperdense right M1 and
eye ischemic changes in the right insula (**Fig. 22.5a**). CT angiogram revealed a
sudden vessel cutoff at the distal M1. Intravenous recombinant tissue plasminogen
activator (rtPA) was administered at 0.6 mg/kg about 2 hours after symptom onset.
Transcranial Doppler revealed persistent occlusion of the right M1 and no change
in neurologic status. The patient was urgently transferred to the interventional
angiography suite.

**Procedure**

Under minimal conscious sedation, a diagnostic angiogram was performed via the
right ICA, which revealed complete occlusion of the inferior branch of the right
MCA and partial spontaneous opening of the superior branch (**Fig. 22.5b**).

A microcatheter was advanced through the occluded inferior MCA branch and
then a retrievable stent was deployed across the occluded segment. A subsequent
right ICA run showed complete opening of the right M1 and M2 branches, but distal
migration of the clot caused an occlusion of the inferior M3 branch (**Fig. 22.5c**). At
this point, 4 mg of intra-arterial rtPA was slowly administered. A right MCA run
revealed complete reopening of the inferior M3 branch but some filling defects
more distally. The retrievable stent was then removed while suction was applied.
Thrombus could be seen entangled in the mesh of the stent. A final angiographic
run showed further opening of the small distal filling defects (**Fig. 22.5d**). The pro-
procedure was then terminated. The time to opening the M2 branch was about 3 hours from symptom onset.

After the procedure, the patient had improved strength in his left upper and lower extremities. Follow-up MRI 3 days later revealed restricted diffusion involving the right caudate head and body, lentiform nucleus, and a few small foci within the right MCA cortical areas. MR angiography revealed continued patency of the right MCA branches. The patient was discharged from the hospital and was able to resume normal activities with ongoing rehabilitation.

Discussion

In patients with acute ischemic stroke, a longer time interval between onset of neurologic symptoms and initiation of treatment is associated with a decreased probability of clinical benefit. The National Institute of Neurological Disorders and Stroke (NINDS) randomized controlled trial of intravenous thrombolysis for ischemic stroke demonstrated clinical benefit if IV rtPA (0.9 mg/kg) was given within 3 hours of symptom onset. This time window was expanded to 4.5 hours after...
onset of neurologic symptoms with the more recent European Cooperative Acute Stroke Study (ECASS III).

This patient had a large vessel occlusion (right M1) and initially received a lower dose of IV rtPA (0.6 mg/kg instead of the traditional 0.9 mg/kg) within the 3-hour time window. Endovascular treatment has a tendency to be more effective in large vessel occlusions like the M1 segment. The lower dose of IV rtPA is a form of bridging therapy to allow an opportunity for vessel recanalization while awaiting setup for endovascular therapy. The lower dose IV rtPA also enables administering more rtPA using the intra-arterial route if vessel occlusion and thrombus is still seen on diagnostic angiogram. Due to the increased risk of hemorrhage, heparin is not administered if rtPA has already been given.

Unlike permanent intracranial stents, a retrievable stent does not require intra-operative or postoperative antiplatelet medications in the form of aspirin or clopidogrel. This reduces the hemorrhage risk, given that the patient already would have rtPA in the systemic circulation. The retrievable stent has the ability to open up a vessel fairly quickly, while at the same time increasing the surface area of the thrombus for the circulating rtPA to act upon.

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**Venous Thrombolysis**

**History**

A 74-year-old man presented with a 1-week history of headache and increasing somnolence. Clinically, he was lethargic and with mild left-sided arm and leg weakness, but otherwise neurologically intact and stable. MRI showed a non-hemorrhagic right thalamic infarct, whereas MR venogram suggested thrombosis of the straight sinus and left transverse sinuses. Intravenous heparinization was administered and the patient was taken to the angiography suite for immediate endovascular venous thrombolysis.

**Procedure**

The procedure was performed under general anesthesia with endotracheal intubation. Femoral artery access on the right and femoral vein access on the left was obtained. Venography demonstrated thrombus of the right sigmoid, transverse, and straight sinus (Fig. 22.6a,b). Working through the venous system, a microcatheter was navigated into the straight sinus. A total of 5 mg of tPA was infused at the rostral end of the straight sinus, followed by an additional 7 mg of tPA infused at 1- to 2-cm intervals as the microcatheter was progressively withdrawn into the transverse and sigmoid sinuses. Following this maneuver, contrast venography was again performed and showed minimally improved flow (Fig. 22.6c).

Subsequently, a Penumbra reperfusion catheter (Penumbra Inc., Alameda, CA) was navigated into the straight sinus, and mechanical aspiration thrombectomy was performed. Again, angiography demonstrated no significant improvement in flow. Finally, the microcatheter was navigated back into the straight sinus, positioned 2 to 3 cm from the rostral end of the thrombus, and left to infuse tPA at 1 mg/hour overnight with concomitant systemic intravenous heparinization. Both the arterial and venous sheaths were left in place, and the patient was kept intubated for anticipated repeat contrast venography the following morning.
The next day, contrast venography demonstrated patency of the straight, transverse, and sigmoid sinuses with excellent flow (Fig. 22.6d). The microcatheter and the venous and arterial sheaths were subsequently removed. Manual pressure was placed on the femoral venous puncture site and a closure device was used for the arterial site.

Minutes later, a hematoma was noted at the arterial puncture site. Pressure was immediately placed over the site. A CT angiogram of the leg was obtained, showing active extravasation of contrast from the puncture site. Systemic heparin was immediately reversed with 50 mg of protamine and manual pressure was maintained on the site for 30 minutes while ensuring the distal pulses remained palpable. Hemodynamic parameters and hemoglobin/hematocrit levels were monitored closely for the next 24 hours and remained stable. Intravenous heparin was restarted 24 hours later and the patient was transitioned to an oral anticoagulation regimen.

**Fig. 22.6a–d**  (a) Anteroposterior and (b) lateral contrast venography showing thrombus within the transverse, sigmoid, and straight sinuses. (c) Lateral venogram showing minimal improvement of the appearance of thrombus after tissue plasminogen activator (tPA) administration through the microcatheter. (d) Lateral venogram performed the following day (after infusion of 1 mg/hour tPA through a microcatheter sitting within the straight sinus) showing resolution of thrombus and significantly improved flow.
Discussion

Based on current evidence, patients with venous sinus thrombosis should be treated with body weight–adjusted low molecular weight heparin or dose-adjusted intra-venous heparin.\(^1\) There is no evidence from randomized controlled trials about the safety or efficacy of local thrombolysis, and local thrombolysis may, in fact, have a higher risk of bleeding complications.\(^2\) Therefore, intravenous heparin should be instituted immediately if no contraindications exist, such as an expanding hemorrhage associated with venous infarction.

In the authors’ experience, good results have been obtained with adjunctive endovascular thrombolysis. If mechanical or chemical thrombolysis fails to reestablish patency of the venous sinuses, a microcatheter can be positioned at 2 to 3 cm from the rostral end of the thrombus and allowed to infuse additional tPA, as was done in this case. A repeat contrast venogram should be performed in 12 to 24 hours to reassess venous flow.

In this case, systemic heparinization during the second procedure likely contributed to hematoma formation at the femoral puncture site. If bleeding at the puncture site is not controlled, the heparin should be reversed immediately with protamine at a dose of 1 to 1.5 mg for every 100 U of heparin administered. The patient should be observed in the intensive care unit and hemodynamic indicators as well as serial hemoglobin/hematocrit levels should be followed closely. As in this case, if postprocedure anticoagulation is required, then intravenous heparin can be restarted, and, if no further bleeding complications occur, the patient can be transitioned to oral anticoagulation or low molecular weight heparin.

Suggested Readings


Risk of Anticoagulants and Antiplatelet Agents in Trauma Patients

Michael C. Huang, Mathieu Laroche, and Geoffrey T. Manley

Trauma is the leading cause of death and disability in children, adolescents, and young adults. Injuries to the central and peripheral nervous systems can lead to disastrous consequences if not treated in a timely manner. Numerous innovations have advanced the field of neurotraumatology in the past few decades, with the goals of diminishing secondary injuries and restoring normal physiology. However, there remains great variability in the management of neurotrauma due to the complexity of neurophysiology, the heterogeneity of lesions, and the lack of randomized controlled studies and comparative effective research.

Patient characteristics and comorbidities are crucial considerations in the initial evaluation of the neurotrauma patient. The assessment of the coagulation parameters in this population is important not only at the time of presentation but also during the entire hospitalization. Coagulopathies can result from deficiencies or disorders of the coagulation pathways, such as hemophilia, thrombocytopenia, or liver disease. Medical therapy with oral anticoagulants, antiplatelet, anti-inflammatory, or chemotherapy agents also contribute to bleeding diatheses. Finally, trauma itself can lead to coagulation abnormalities.

Currently, more than 1% of the population receives oral anticoagulation therapy for various cardiovascular conditions. Although several recent studies have focused on traumatic brain injury (TBI) in patients receiving anticoagulation and antiplatelet therapies, there are no strict guidelines regarding the management of these complex patients. The literature, composed mostly of retrospective studies, has shown conflicting results regarding TBI in the setting of preinjury anticoagulation and antiplatelet usage, with a trend toward worse outcome. The management of these patients raises multiple questions regarding initial blood testing and imaging, reversal of anticoagulant agents, timing of follow-up imaging, and resumption of the oral anticoagulants or antiplatelet therapies.

Anticoagulant and Antiplatelet Agents

Anticoagulation therapies are commonly indicated for the prevention of thromboembolic complications of atrial fibrillation, deep venous thrombosis, pulmonary emboli, extracranial vascular disease, prosthetic heart valves, ischemic stroke, and ischemic heart disease. The most frequently used medication is warfarin, an oral anticoagulant that inhibits vitamin K–dependent clotting factors. Therapeutic monitoring is crucial with warfarin administration, as it has numerous interactions with food and medications. Advanced age and concomitant diseases can also affect its metabolism. Low molecular weight heparin (LMWH) is occasionally used instead of warfarin, especially as a bridging therapy in certain clinical conditions.
Antiplatelet agents are indicated for the primary and secondary prevention of stroke and ischemic heart diseases. The two most commonly used medications are aspirin, an irreversible inhibitor of cyclooxygenase-1 (COX-1), and clopidogrel, an adenosine diphosphate (ADP) receptor antagonist and platelets aggregation inhibitor. Nonsteroidal anti-inflammatory drugs (NSAIDs), which are frequently taken for mild pain, also possess mild antiplatelet properties.

Direct thrombin inhibitors (DTIs) are a new class of oral anticoagulation medication that was recently approved by the Food and Drug Administration (FDA) for the prevention of thromboembolism in atrial fibrillation. Dabigatran etexilate has a predictable pharmacokinetic profile allowing a fixed dose to be given without the need to monitor the anticoagulation status.1

Specific Risks Associated with Preinjury Anticoagulation or Antiplatelet Therapies

Spontaneous intracranial hemorrhage is a well-known complication of long-term anticoagulation therapy, with an annual risk of 0.3 to 0.6%.2 In a meta-analysis by Linkins et al,3 21% of the major bleeds associated with anticoagulation were ICHs. Intensity of anticoagulation (international normalized ratio [INR] > 4), increased variations in INR, and advanced age have been associated with increased risk for ICH.2 There is conflicting data regarding outcomes following TBI in the setting of prehospital antiplatelet and anticoagulant therapies. The results are confounded by the retrospective nature of the study series, the heterogeneity of patient populations, and the inconsistencies in the categorization of injury patterns and clinical classifications. There appears to be a trend toward higher morbidity and mortality associated with TBI in patients taking anticoagulation or antiplatelet agents. These results, however, need to be confirmed with prospective studies.

Traumatic Brain Injury and Warfarin

Spontaneous ICHs associated with warfarin therapy with an INR greater than 3.0 are associated with a larger hematoma size, higher probability of hematoma progression in the first 24 to 48 hours, and delayed hematoma expansion up to 7 days when compared with spontaneous ICH in the absence of anticoagulation.4–6 Several retrospective studies have shown an up to five times increased risk of mortality in warfarin-treated patients after TBI when compared with non-anticoagulated patients.7–10 However, similar results were not seen in other larger observational studies.11–13 Age and initial Glasgow Coma Scale (GCS) score continue to be the most important predictors of mortality and outcome in the trauma population.

There is a trend toward clinical and radiological deterioration in patients receiving preinjury warfarin therapy who present with an abnormal head computed tomography (CT) but good neurologic status. Although these patients may appear to have only mild head injury, they are at high risk of delayed neurologic deterioration, and rapid correction of INR may lead to a lower mortality in these patients.9,10,12,14 A retrospective study by Howard et al15 found that preinjury warfarin therapy had the greatest negative impact on mortality in elderly patients who presented with an initial GCS of 14 to 15 after a fall. These patients had a 25% chance of positive findings on head CT and a 2.3 increase in mortality compared with those without preinjury anticoagulation.
Several retrospective studies have analyzed the effects of preinjury antiplatelet therapy in TBI patients. These studies have demonstrated conflicting results due to their retrospective nature, variability in the antiplatelet agents, and the inability to objectively quantify the effects of antiplatelet agents. Several studies have shown increased mortality risk with antiplatelet agents, whereas others have shown no higher risk when adjusted for age and severity of injury. A recent retrospective study by Siracuse et al. found that traumatic ICH in patients taking antiplatelet agents has increased 5-fold in 2007–2008 compared with 1999–2000. The mortality rate in the antiplatelet group was 17%, which is similar to the mortality rate associated with warfarin therapy. Similar results were obtained in a retrospective study examining 109 trauma patients taking antiplatelet therapy with evidence of ICH on the initial head CT. These patients were more likely to present with a higher grade of hemorrhagic injury and have a higher mortality rate (18%) than did similarly injured patients not receiving antiplatelet therapy (Fig. 23.1). Interestingly, the high mortality was not caused by hemorrhage progression (as in warfarin patients) but by either the severity of the hemorrhage at the time of injury or the exacerbation of other medical conditions.

![Fig. 23.1a,b](image) Progression of intracranial hemorrhage with preinjury antiplatelet therapy. An 81-year-old man with syncope and a fall from the standing position. (a) Initial noncontrast head computed tomography (CT) showed bifrontal contusions and subarachnoid hemorrhage. (b) Follow-up noncontrast head CT 3 hours later after neurologic deterioration showed enlargement of contusions. The patient was later found to be taking prasugrel (a third-generation oral thienopyridine).
Management of a Traumatic Brain Injury Patient Receiving Antiplatelet or Anticoagulation Therapy

The management of patient with suspected TBI receiving antiplatelet or anticoagulation therapy must take into account the mechanism of injury, and the complete history and physical examination, including any loss of consciousness (LOC), seizure, headache, nausea or vomiting, or focal neurologic deficits (Fig. 23.2). A high index of suspicion is warranted, and there should be a low threshold for obtaining cerebral CT imaging even in the absence of LOC or focal neurologic findings. In fact, the American College of Emergency Physicians specifically recommends a head CT in the presence of coagulopathy. Some studies have found that anticoagulated patients with an initial GCS of 15 and a normal head CT were still at risk of delayed neurologic deterioration and should be observed for 12 to 24 hours with frequent neurologic assessments. Patients with TBI, especially those with pre-injury anticoagulation or antiplatelet therapy, should be admitted to the intensive care unit (ICU) and managed as per the Brain Trauma Foundation guidelines.

Fig. 23.2 Management of patients with preinjury antiplatelet or anticoagulation therapies. BTF, Brain Trauma Foundation; CBC, complete blood count; CT, computed tomography; FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalized ratio; PCC, prothrombin complex concentrate; PTT, partial thromboplastin time; STAT, at once; T&S, type and screen.
Any positive finding on the head CT should prompt the reversal of anticoagulation or antiplatelet therapy. Infusion of fresh frozen plasma (FFP) at 15 mL/kg and vitamin K injections can be used for correction of coagulopathy secondary to warfarin therapy. Platelets should be transfused for those receiving antiplatelet therapy. In patients requiring emergency neurosurgical procedures, including invasive neuromonitoring, the administration of prothrombin complex concentrate (PCC) or activated factor VIIa should be considered (Fig. 23.3). These agents have been shown to be safe and can normalize the INR quicker than the administration of FFP. Patients with preinjury antiplatelet therapy should receive at least six units of platelets at the time of the procedure, and activated factor VIIa may also be considered if profuse bleeding is seen during the operative procedure. Currently, there is no antidote to reverse the effects of DTIs, though hemodialysis, activated factor VIIa, and PCC may be considered during emergencies.

Although there are no established guidelines regarding follow-up imaging, it is common practice to repeat cerebral imaging 6 to 24 hours after the first positive radiographic findings. Changes in neurologic examination or neuromonitoring should prompt reevaluation with appropriate radiographic testing.
Timing for Resuming Anticoagulation After Traumatic Brain Injury

There is currently no guideline for determining the optimum timing for the reintroduction of anticoagulation or antiplatelets therapy after traumatic ICH. The indications for anticoagulation and the risks of withholding treatment must be weighed against the risks of rebleeding on an individual basis. Although most authors feel that it is generally safe to resume anticoagulation after of 1 to 2 weeks, some advocate waiting 10 to 30 weeks. A common practice is to repeat cerebral imaging before and after the reintroduction of anticoagulation and to use preferentially anticoagulant medications that can be reversed. The patient should be observed closely following the resumption of anticoagulation.

Chronic Subdural Hematoma

Chronic subdural hematoma (CSDH) is frequently seen in elderly patients and is thought to be the result of a traumatic tear in a parasagittal vein. Surgical treatments include bedside drainage, bur hole evacuation, and craniotomy. CSDHs have high rates of recurrence, ranging from 9.2 to 26.5%, often necessitating repeat evacuations. The incidence of CSDH and the risk of reaccumulation following evacuation in patients receiving antiplatelet or anticoagulation therapy are unclear. Anticoagulation usage seems to be more frequent in patients presenting with CSDH without any obvious history of head trauma. However, the overall mortality and morbidity did not appear to be affected. The recurrent rate of CSDH following evacuation appears to be higher in patients maintained on antiplatelet therapy before surgery. Patients receiving warfarin therapy, whose coagulopathies were normalized prior to surgery do not appear to be at elevated risk for reaccumulation of their CSDH. Some attribute this difference to the difficulty of reversing antiplatelet agents versus warfarin therapy. However, given the heterogeneity the study populations, definitive recurrence rates cannot be determined. Follow-up imaging should be strongly considered, especially in those receiving antiplatelet treatment.

The timing of reintroduction of antiplatelet or anticoagulation therapy after successful surgical treatment of CSDH is also unclear. In the majority of patients, the associated risk of withholding the medication seems to be low. A period of 3 to 8 weeks before the reintroduction of anticoagulation is often cited in the literature, but this delay should be personalized according to the indication for anticoagulation in each patient. Even in a high-risk patient (cardiac valve replacement), stopping anticoagulation for 1 to 2 weeks appears to be safe. A follow-up imaging before the reintroduction of anticoagulation is a common practice.

Traumatic Spinal Hemorrhage

Although spine fractures are common findings following trauma, the exact incidence of posttraumatic spinal hematoma is difficult to assess. Posttraumatic epidural hematoma is reported in 52% of patient with spine fracture when a magnetic resonance imaging (MRI) scan is ordered within the first 48 hours. The 6-month prognosis is the same in patient with spinal fractures, with or without epidural hematoma. According to a meta-analysis of 613 patients with spinal hematomas,
the localization of spinal hematomas is mostly epidural (75%), follow by subdural/subarachnoid (20%), and intraparenchymal in less than 1%. Anticoagulation was the etiology in 17% of the patients, representing the second most common cause of spinal hematoma. Anticoagulation with warfarin was the most common culprit, rather than antiplatelet agents. Clinically significant posttraumatic spinal hematoma was found in 10% of patients. Of these, 55% were associated with spinal fractures. The majority of cases were cervicothoracic or thoracolumbar epidural hematoma.

Most patients with spinal hematoma present with acute back pain, with or without radiculopathy, that progresses rapidly to a sensorimotor deficit. An MRI scan is the gold standard exam to delineate the location and anatomy of the hematoma. Emergency reversal of anticoagulation with timely surgical management including laminectomy with evacuation of the hematoma and spinal cord decompression offer the best chance of neurologic recovery. A complete recovery is expected in 40% of patients, and 34% will have a mild to severe neurologic deficit. The two most important prognostic factors are the preoperative neurologic status of the patient and the timing of the surgery. Early surgery within 24 hours offers the best chance of recovery, with the greatest recovery if decompression is performed within 8 hours. Although recovery after 24 hours is unlikely, some studies have demonstrated neurologic improvements even following decompression after 48 hours.

The timing of the resumption of anticoagulation in this population has not been systematically studied, but most authors recommend waiting for 7 to 14 days after surgery, with special attention to the neurologic exam when anticoagulation is reinitiated.

Traumatic Nerve Injury Associated with Antiplatelet or Anticoagulation Therapy

There is a paucity of studies regarding the risk of peripheral nerve injury associated with treatment with antiplatelet or anticoagulation therapy. Most of the literature is composed of case reports and small series of patients presenting with spontaneous hematoma causing direct compression of peripheral nerves or plexus.

Retroperitoneal hematoma, whether spontaneous or posttraumatic, has been known to occur in patients receiving anticoagulation or antiplatelet therapy. The hematoma is usually located in the iliacus muscle or in the retroperitoneal space and causes direct compression on the lumbosacral plexus. Patients present with acute onset of severe groin/abdominal pain followed by a variable picture of femoral neuropathy including numbness in the anteromedial thigh and weakness in the iliopsoas and quadriceps muscle. The diagnosis is made by abdominal ultrasound, abdominal pelvic CT, or MRI. Although the treatment is controversial, most authors agree that surgical drainage of the hematoma (ultrasound guided or through a limited retroperitoneal incision) offers the best chance of recovery in the presence of progressive neurologic deficit. The coagulopathy should also be reversed using the appropriate treatment.

Other forms of compressive neuropathy such as acute carpal tunnel syndrome has also been described in anticoagulated patients. Although infrequent, significant bleeding and neurologic injury have been reported following regional anesthesia involving peripheral nerve, brachial, and lumbosacral plexus, and paravertebral blocks. Strict recommendations for regional anesthesia in patients under antiplate-
let or anticoagulation therapy have been published and are beyond the scope of this chapter.45

Conclusion

Increasing numbers of patients treated with antiplatelet or anticoagulation therapies are being evaluated after sustaining neurotrauma. These patients must be considered at high risk for neurologic deterioration, and any suspicion of injuries to the central nervous system must be dealt with promptly. Currently, no guideline exists for the management of these complex patients due to the lack of level 1 evidence. For patients receiving anticoagulation with warfarin who have suffered a traumatic lesion to the nervous system, the coagulopathy should be reversed using FFP and vitamin K. If an emergency neurosurgical procedure is indicated, rapid normalization of the INR may be achieved with the administration of PCC or activated factor VIIa. However, their use in trauma has never been compared with FFP and vitamin K in a randomized controlled study. The management of patients receiving antiplatelet therapy is less clear. Transfusion of platelets will reduce bleeding in unstable patients or if an emergency neurosurgical procedure is necessary. After the acute event, the decision to resume anticoagulation therapy should be considered on individual basis, and the indications, risks, and benefits of those treatments must be taken into account. Repeat imaging before and after resumption of the anticoagulation and antiplatelet therapies should be considered. Overall, more prospective research and comparative effectiveness research are needed to address these important questions.

KEY POINTS

• The literature concerning the use of preinjury antiplatelet and anticoagulation therapy in nervous system trauma is mostly retrospective and confounded by the heterogeneity of the studied populations and the study methods.

• An extremely high index of suspicion is imperative in patients receiving antiplatelet or anticoagulant therapy who have sustained traumatic injuries, as they are at high risk of neurologic deterioration.

• The rapidity of the reversal of the coagulopathy must take into account the neurologic state of the patient, the radiological findings, and the need for emergency neurosurgical procedure.

• Resuming anticoagulation following neurotrauma should take into account indications, risks, and benefits of the therapy and imaging before and after the initiation of the treatment is strongly recommended.
REVIEW QUESTIONS

1. A 64-year-old man suffers a fall at home striking his head. His GCS score is 14. He is taking ASA daily and his head CT shows no hemorrhage. What is the most appropriate course of treatment?
   A. Administration of 6 units of platelets
   B. Admission to the ICU for observation
   C. Administration of FFP
   D. Administration of activated factor VIIa
   E. Discharge home

2. A 70-year-old woman with a prior history of venous thromboembolism is in a motor vehicle accident. Her GCS score is 15. She is on warfarin for her history of deep venous thrombosis/pulmonary embolism. A head CT demonstrates a small frontal contusion. Which of the following is most appropriate for administration?
   A. Activated factor VIIa
   B. Fresh frozen plasma (FFP) and vitamin K
   C. Six units of platelets
   D. Protamine sulfate

3. In which of the following clinical instances is the risk of reaccumulation of a chronic subdural hematoma greatest?
   A. Anticoagulation use prior to presentation, which was reversed at the time of surgery
   B. Antiplatelet agents prior to surgery
   C. Diabetes mellitus
   D. Hypertension

4. Following spinal trauma, what is the most common location for a spinal hematoma?
   A. Epidural
   B. Intraparenchymal
   C. Subarachnoid
   D. Subdural

5. A 40-year-old man presents with acute thoracic back pain after a fall. X-rays are negative for fracture or dislocation. He then develops progressive weakness in his legs. What is the most appropriate diagnostic test to do next?
   A. CT scan thoracic spine
   B. MRI thoracic spine
   C. Spinal angiogram
   D. Spinal ultrasound

6. All of the following are known to increase the likelihood of recovery following a compressive spinal hematoma except:
   A. Early surgery for evacuation and decompression
   B. Reversal of anticoagulation
   C. Less neurologic deficit prior to surgery
   D. Administration of steroids
References


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Management of patients undergoing cranial surgery involves all aspects of coagulation and bleeding, both positive and negative. This chapter presents specific cases to highlight these issues.

Case 1: Catastrophic Intracerebral Hemorrhage Associated with Dabigatran

An 83-year-old man suffered a ground-level fall at home. There was no loss of consciousness. Upon arrival in the emergency room, he complained of nausea, but his Glasgow Coma Scale (GCS) score was 15.

He had been started on dabigatran (oral direct thrombin inhibitor) 1 month prior to admission for new-onset atrial fibrillation. His admission laboratories demonstrated a hematocrit of 41 and normal platelet count. His prothrombin time (PT)/international normalized ratio (INR) was 17.2 seconds/1.4, and his partial thromboplastin time (PTT) was 43 seconds. His thrombin time was > 150 seconds (normal 14.7–19.5).

His initial computed tomography (CT) scan (Fig. 24.1a,b) demonstrated relatively minor subarachnoid hemorrhage and contusions. He was admitted to the Neurocritical Care Unit, and Keppra was started for seizure prophylaxis.

Approximately 2 hours later, he became aphasic and a repeat CT was performed (Fig. 24.1c,d), which demonstrated interval increase in intracerebral hemorrhage bilaterally. He was administered a weight-based dose of factor VII. He became increasingly somnolent, and a follow-up CT was performed 4 hours following admission (Fig. 24.1e,f), which demonstrated significant evolution of intracerebral hemorrhage. At the family's wishes, no further treatment was offered and he expired from his intracerebral hemorrhage.

Discussion

Dabigatran is a synthetic, oral direct competitive thrombin inhibitor; 80% of the drug is excreted renally. Serum half-life is 12 to 17 hours, and the drug does not require routine monitoring with INR. There is no direct antidote; hemodialysis can remove 60% of the circulating drug. The administration of factor VIIa may help (it did not alter the outcome in this unfortunate case), but fresh frozen plasma (FFP) and vitamin K administration are not effective.

Although the option of dialysis was discussed in this case, the ability to perform rapid dialysis, even in a trauma center, is problematic.
Case 2: Hemorrhage Associated with Sagittal Sinus Thrombosis

A 53-year-old man presented with a 6-week history of progressively worsening headaches. His GCS was 15 and he had a normal neurologic examination except for papilledema. A CT head and magnetic resonance imaging (MRI) scan were performed, which identified a heterogeneously enhancing right parasagittal frontal lobe lesion with significant surrounding edema (Fig. 24.2a). The presumptive diagnosis was a primary brain tumor, most likely glioblastoma multiforme (GBM).

The patient’s admission laboratories were normal. He was started on Decadron, resulting in quick symptom relief. Surgery was performed to resect the lesion, which was uneventful. However, the lesion was more consistent with an old hematoma, and a thrombosed cortical vein was identified extending from the area of the lesion to the sagittal sinus. Frozen section pathological examination and final pathology demonstrated no tumor, only evidence of hemorrhage and necrosis. There was no evidence of thrombus on the initial MRI scan. Fig. 24.2b shows the region of the posterior sagittal sinus, which is free of thrombosis. The postoperative MRI scan done 24 hours later identified thrombus in the superior sagittal sinus.

In a patient taking dabigatran, the PT/INR is usually not affected. Similarly, the PTT is not elevated. The thrombin time (TT) and ecarin clotting time (ECT) are sensitive to the drug, and a normal TT and ECT exclude the presence of significant dabigatran levels.

Fig. 24.1a–f (a,b) Initial computed tomography (CT) scan demonstrating subarachnoid hemorrhage (SAH) and contusions. (c,d) Two hours after admission, CT demonstrates significant bilateral increase in hemorrhage. (e,f) CT performed 4 hours after admission demonstrates massive bilateral increase in hemorrhage.
The patient was started on low-dose unfractionated heparin immediately postoperative. Full-dose intravenous (IV) heparin was started 24 hours after his craniotomy. Heparin was then converted to warfarin starting on the 5th postoperative day. He suffered no complications from the anticoagulation, which was continued for 6 months. Follow-up MRI demonstrated complete recanalization of his venous sinuses. After discontinuing warfarin, the patient underwent testing for risk factors for hypercoagulability, all of which were negative.

**Discussion**

This patient's presentation was somewhat atypical but was totally secondary to venous thrombosis and hemorrhage. The intraoperative findings and postoperative MRI established the diagnosis. There was no definite evidence of sagittal sinus thrombus on the preoperative MRI. The appropriate treatment for cranial venous thrombosis is anticoagulation. He remained clinically stable in the early postoperative period, and there was no evidence of any deep venous involvement. He was started on subcutaneous heparin immediately, to provide some effect on thrombus progression. Full-dose IV heparin therapy was withheld until 24 hours postoperatively, in recognition that this represented a risk for thrombus progression, but also trying to balance the risk associated with full anticoagulation in a patient who has just had a craniotomy.
Case 3: Intracerebral Hemorrhage Associated with Edoxaban

A 74-year-old man with Parkinson disease who was increasingly impaired by motor fluctuations underwent an uncomplicated placement of a left subthalamic nucleus deep brain stimulation (DBS) electrode for control of his symptoms. Following surgery his symptoms dramatically improved and he was able to reduce his Parkinson medications, and a postoperative CT scan (Fig. 24.3a) demonstrated good electrode placement.

Fig. 24.3a–d  (a) Immediate postoperative CT scan demonstrating left deep brain stimulation (DBS) electrode in the subthalamic nucleus (STN). (b) MRI (T1-weighted) done 4 months postoperatively demonstrates subacute hemorrhage along the DBS electrode. (c,d) CT scan done 1 week after MRI demonstrating significant interval hemorrhage around the tip of the electrode.
Intraoperative Cranial-Specific Patient/Case Examples

Following surgery, he was started on a newer factor X inhibitor, edoxaban, for treatment of atrial fibrillation. Approximately 4 months after surgery he developed a decline in cognitive function and speech difficulty. A subacute hemorrhage with mixed signal intensity was noted along the brain lead on the T1-weighted MRI (Fig. 24.3b).

One week later he developed worsening of memory problems, and a repeat study showed significant interval hemorrhage around the tip of the electrode on a CT scan (Fig. 24.3c,d). The edoxaban was discontinued. He was left with residua of mild residual aphasia and diplopia.

Discussion

Edoxaban is an anticoagulant drug that acts as a direct factor Xa inhibitor. It is potent, selective for factor Xa, and has good oral bioavailability. It was initially approved in July 2011 in Japan for prevention of venous thromboembolism (VTE) following lower-limb orthopedic surgery. The advantages of orally administered direct factor Xa inhibitors lie in the fact that they have a predictable effect, do not require frequent monitoring or re-dosing, are taken orally, and have few known drug interactions.

More recently, once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism, and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

Neurosurgical experience with these newer factor Xa inhibitors is lacking. This case is of particular interest as the patient was enrolled in a trial for this drug in the treatment of atrial fibrillation, and the DBS electrode was not considered a contraindication for treatment.

A recent study has indicated that recombinant factor VIIa (rFVIIa), prothrombin complex concentrate, and activated prothrombin complex concentrate have the potential to be reversal agents for edoxaban.

Case 4: Trauma in a Patient with Alcoholism (Subacute Presentation)

A 55-year-old man presented with confusion cycling with somnolence and agitation. He had a known history of alcoholism and was intoxicated. He had bruising over his forehead and around his right eye. His blood alcohol level was 200 mg/dL. A CT head (Fig. 24.4) was done in the emergency room because of concern about his overall level of consciousness that demonstrated a right frontal intracerebral hemorrhage ICH) and contusion with significant surrounding low-density change with effacement of the right lateral ventricle frontal horn. In addition there was a modest amount of anterior interhemispheric subdural blood and some subarachnoid blood. The ICH extended to the inferior part of the frontal lobe. A CT angiogram was completed because of the definitive trauma history and did not identify any vascular abnormality. His level of consciousness improved, and on examination (after the CT) his GCS score was 14.

His admission laboratories demonstrated a hemoglobin of 10.2 g/dL and platelet count of 67,000/micromole. His INR was 3.1, and PTT 50 seconds. He was on no known anticoagulation medications. His γ-glutamyltransferase (GGT) was 2,376 U/L.
Management and Discussion

He was treated conservatively regarding the ICH. It was felt that the hemorrhage was subacute and likely traumatic, and that he was at low risk for clinical deterioration from the current mass effect. The goal was to prevent further bleeding, reduce the probability of seizure, and manage his alcohol abuse and his liver disease. He was treated with Dilantin (dose adjusted to deal with liver dysfunction) and received supportive and prophylactic medications to manage alcohol withdrawal. He received vitamin K 5 mg IV and 4 units of FFP. After the FFP infusion, his INR improved to 2.2. The goal was not to attempt to normalize his INR but to improve his circulating coagulation factor levels in the short-term while the state of his liver disease was determined via consultation with the gastroenterology service. Prothrombin complex concentrate (PCC) was not felt to be required in this situation but could be an option if he was presenting with a more acute and severe deterioration relating to the ICH and especially if surgery was required. Although he had thrombocytopenia, his platelet count was not low enough to warrant intervention. The gastroenterology consultants directed nutritional therapy recommendations.

He remained clinically stable with regard to the ICH. However, the overall effects of chronic alcohol abuse combined with the new traumatic brain injury were quite significant, and he eventually required transfer to an extended care facility.

Case 5: Patient with Suspected Idiopathic Normal Pressure Hydrocephalus and Low Platelet Count

An 85-year-old man presented with a 12-month history of progressively worsening gait, cognitive deterioration, and bladder urgency progressing to incontinence. He had previously been well and independent before his symptoms started, but was now at a point that one-person assist was required to transfer, and he primarily
used a wheelchair. His Montreal Cognitive Assessment (MoCA) score was 19/30, confirming significant cognitive disability. His MRI identified ventriculomegaly (Fig. 24.5). His clinical diagnosis was compatible with idiopathic normal pressure hydrocephalus (iNPH).

Investigations would typically involve either a large-volume lumbar puncture (LP) or extended lumbar drainage (ELD) of cerebrospinal fluid (CSF). Both are provocative tests to assess whether removal of CSF improves gait or cognitive function to determine if the patient is a candidate for treatment with a ventriculoperitoneal shunt.

This patient's screening laboratory tests were normal with the exception of a platelet count of 59,000/micromole. Hemoglobin was at the low end of normal. The hematology service was consulted, and the patient received a platelet transfusion in preparation for insertion of a lumbar drain. However, his platelet count dropped to 49,000/micromole after the platelet transfusion and the lumbar drain was canceled. Further investigations resulted in a diagnosis of chronic idiopathic thrombocytopenic purpura (ITP). After further discussion with the patient and family, in conjunction with the hematologist, it was decided not to pursue further investigation or possible treatment of his hydrocephalus.

This patient's potential condition (iNPH) would require investigations and treatment that would be high risk given his diagnosis of ITP. Although therapies for ITP are possible, it was the opinion of the hematology service that it would be extremely challenging, given his age and other comorbidities, to have any significant effect on his disease process. Neither the patient nor his family wished to pursue any treatment of the ITP or further investigation or treatment of the possible hydrocephalus.

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**Case 6: Patient with Suspected Idiopathic Normal Pressure Hydrocephalus on Warfarin for Atrial Fibrillation**

A 78-year-old man presented with an 8-month history of progressively worsening gait, cognitive deterioration, and bladder urgency progressing to incontinence. He
had previously been well and independent before his symptoms started, but was now at a point of requiring a cane to walk. The MoCA score was 23/30, confirming moderate cognitive disability. A CT of the head identified ventriculomegaly (Fig. 24.6a). His clinical diagnosis was compatible with iNPH.

He had a history of atrial fibrillation (AF) that was clinically stable and had no previous history of myocardial infarction. He was on warfarin, and the INR was 2.6. Warfarin was stopped 5 days prior to his admission for extended lumbar drainage. The INR was 1.1 on the day of admission. Bridging with low molecular weight heparin (LMWH) was not undertaken for this patient.

Fig. 24.6a–d  (a) Preoperative CT scan demonstrating ventriculomegaly. (b) Postoperative CT scan demonstrating normal ventricular catheter placement and no hemorrhage. (c) One month postoperative CT scan showing ventricular collapse and bilateral chronic subdural hematomas (CSDHs). (d) One month after catheter drainage of left chronic subdural hematoma (two months after shunt insertion). Valve is set to 2.5.
He underwent ELD of CSF to assess whether removal of CSF would improve his gait or cognitive function, and to determine if the patient was a candidate for treatment with a ventriculoperitoneal (VP) shunt. He experienced a significant improvement in his gait function observed over laps of a 10-m distance (time, number of steps, number of steps to turn). The MoCA improved to 25/30. Surgery to insert a ventriculoperitoneal shunt was recommended, and the patient and his family agreed to proceed. A VP shunt with a Strata® (programmable) valve (Medtronic, Elizabeth, NJ) was implanted without any early postoperative problems. A postoperative CT scan demonstrated good catheter placement and no evidence of bleeding (Fig. 24.6b).

He continued his clinical improvement, developing the ability to walk independently without a cane. Warfarin was restarted on postoperative day 4 and the INR was therapeutic on postoperative day 9 (INR = 2.4). He was discharged to home with outpatient physiotherapy and occupational therapy. He presented for his first postoperative follow-up 4 weeks after surgery and 2 weeks after discharge from hospital, and continued to improve with regard to his gait, cognition, and urinary urgency/frequency. However, a CT head scan demonstrated bilateral chronic subdural hematomas (CSDHs) with the left greater than the right (Fig. 24.6c).

He was admitted to the hospital and received vitamin K 2 mg IV, and his valve was adjusted to a setting of 2.5 from an initial setting of 2.0. The INR corrected by day 4 and he underwent insertion of a left subdural drain under local anesthesia. The drain was removed after 24 hours, and although he was not as clinically well as when the shunt was fully functional, he nevertheless remained at a higher function level than he was prior to the shunt. Warfarin was not immediately restarted. He was discharged home, and at an assessment 4 weeks after the treatment of the CSDH, he remained stable and CTs of the head continued to improve (Fig. 24.6d), although he was still demonstrating a much smaller left CSDH and a very small right CSDH. The valve setting was left at 2.5.

Over a total period of 3 months, the CSDHs completely resolved. The valve was then reset to 2.0 with further clinical improvement. Warfarin was restarted (after additional consultation with a cardiologist) at that time, and the patient remains clinically stable 2 years post–ventriculoperitoneal shunt insertion with no reaccumulation of the CSDHs.

Discussion

This patient represents a common problem in neurosurgery. A significant number of elderly patients are being treated with anticoagulation because of atrial fibrillation. In many, the agent (typically warfarin) can be stopped before any surgical procedure without the need for bridging therapy with a LMWH agent. In this patient, the warfarin was restarted after the ventriculoperitoneal shunt was inserted and he developed bilateral CSDHs. He was clinically well, but because of the anticoagulation and the size of the left CSDH, he was admitted to the hospital and, after turning his valve up to maximal resistance and reversal of his warfarin effect with vitamin K, he underwent treatment of the CSDH. In this situation, the process was successful and the shunt did not require ligature occlusion of the peritoneal catheter. Warfarin was not restarted until the CSDHs had completely resolved, and he had successfully responded to a reduction in valve resistance.
References


Several unique aspects of spinal surgery require surgeons to have a working knowledge of the nuances of perioperative anticoagulation and antiplatelet management. First, spine surgical procedures have the potential for significant blood loss secondary to the abundant vascular supply to the paraspinal and vertebral structures, as well as the ongoing osseous blood loss that routinely occurs with complex and multilevel fusion procedures. Second, postoperative spinal surgery patients routinely have periods of prolonged absent or limited mobility. Third, postoperative hemorrhage adjacent to the spinal cord has the potential to cause significant or permanent neurologic disability. Taking these points together, decision making related to the use of perioperative anticoagulation and antiplatelet agents requires careful consideration of a complex risk to benefit ratio, such that the incidence of intraoperative or postoperative hemorrhage is balanced against the risk of perioperative venous thromboembolism (VTE) to optimize spinal surgery patient outcome.

Accordingly, this chapter provides an overview of the medical literature as it pertains to anticoagulants and antiplatelet agents, discusses the risks of spontaneous spinal hemorrhage in both the general population and in patients with disorders of the spinal column and spinal cord, and discusses the risks and benefits in the perioperative spinal surgery population.

**Anticoagulation and Spontaneous Spinal Hemorrhage**

**Risk of Anticoagulant or Antiplatelet Agents as a Source of Spontaneous Spinal Hemorrhage in the General Population**

The most significant spinal complication resulting from systemic anticoagulant or antiplatelet therapy is spontaneous spinal hemorrhage (SSH). This complication, though rare, must be considered in patients with elevated coagulation cascade times (prothrombin time [PT]/partial thromboplastin time [PTT]) who present with local or referred spinal pain associated with neurologic deficits. In these patients, an urgent magnetic resonance imaging (MRI) is vital to confirm the diagnosis. Spinal hemorrhage may vary in location by anatomic compartment. Spinal epidural hematoma (SEH) is the most common SSH type and accounts for 75% of all such hemorrhages, whereas subdural and subarachnoid bleeding occur with much less frequency; hematomyelia, or bleeding within the spinal cord, is very uncommon.1

The estimated incidence of SSH in the general population is very difficult to delineate but is known to be very low. As of 1996, there had only been 613 total reported cases. Kreppel et al,2 in the most comprehensive SSH review to date, per-
formed a meta-analysis of these 613 patients. In their analysis they noted that 29.7% of spontaneous spinal hemorrhage was idiopathic in origin, whereas medicinal anticoagulation was recognized as the second most common etiology and accounted for 17% of SSH occurrences. Interestingly, given that patient anticoagulation could be implicated in only a minority of SSH instances, Kreppel et al speculated that anticoagulation alone is likely to be insufficient to promote SSH without an additional factor such as elevated vertebral venous plexus pressure. To further support the notion that anticoagulation is an exceedingly rare cause of SSH, Angstwurm and Frick found a frequency of spinal hematoma of only 1% in 10,441 patients who experienced hemorrhage of any type while on therapeutic anticoagulation. Another study found no spinal hemorrhage among a total of 3,126 patients who were followed for any complication of anticoagulation therapy. Thus, due to the extremely low incidence of SSH combined with a lack of high-quality data, it is not possible to define the specific relative risk of developing an SSH while on anticoagulation therapy. However, based on the available retrospective population studies, the risk would appear to be very low (<1%) in patients with well-controlled anticoagulation therapy, and is likely not statistically more probable to occur than that in the general nonanticoagulated population.

**Risk of Anticoagulant or Antiplatelet Agents as a Source of Spontaneous Spinal Hemorrhage in Patients with Spinal Column or Spinal Cord Disorders**

Broadly, disorders of the spinal column or spinal cord can be categorized as traumatic injury of the spinal column or spinal cord injury (SCI), degenerative or spondylotic conditions, deformity, neoplasm, infection, or vascular lesions of the spine or spinal cord. In our review we attempted to determine the risks of anticoagulant and antiplatelet agents in the context of these various categories of spinal disorders. Unfortunately, there is a paucity of studies delineating the relative safety of anticoagulant or antiplatelet agents in the setting of distinct spinal pathologies. Spondylotic or degenerative spinal disorders have a very high population prevalence and accordingly warrant specific discussion. In our review, we found no evidence to suggest that degenerative spinal disease inherently increases the risk of spinal hemorrhage in patients requiring therapeutic anticoagulation beyond the general population receiving anticoagulation. Similarly, there is no evidence that patients with spinal deformity are at an increased risk of spinal hemorrhage in the face of anticoagulant therapy. Thus, patients with spinal degenerative disease or deformity can be placed on anticoagulants or antiplatelet agents as indicated for other pertinent medical conditions.

Although there are anecdotal reports of spontaneous spinal hemorrhage in patients with spinal neoplasms on anticoagulants, given the sporadic case report nature of these data, there are no guidelines for management in this situation. However, as will be discussed in detail in a later section, it is clear that patients with malignant disease are at a high risk of VTE, and thus the risk-to-benefit ratio, although difficult to quantify specifically, would appear to be highly in favor of initiation of anticoagulant therapy as indicated for other medical conditions.

Spinal vascular malformations are very uncommon entities and intuitively may be perceived to have an increased relative risk of spinal hemorrhage in the setting of anticoagulation therapy. Interestingly, the medical literature contains no description of the relative risk of hemorrhage from a spinal vascular malformation...
while being anticoagulated. Accordingly, one must balance the natural history of the disease requiring anticoagulation versus the apparent very low increase in risk of spinal vascular malformation hemorrhage.

Anticoagulation and Spinal Surgery

Consideration of anticoagulants and antiplatelet agents in the perioperative spinal surgery patient population requires the treating surgeon to weigh the often-complex balance of risks of postoperative spinal hematoma formation versus the distinct benefits of preventing VTE complications. Spinal surgery interventions occur for distinct pathologies over a wide spectrum of invasiveness and complexity and, accordingly, it is intuitive to consider that the risk-to-benefit profile similarly will vary widely over this spectrum of underlying etiology and surgical complexity.

Accordingly, spinal surgery procedures are often typically divided into simple and complex spinal procedures. Simple spinal procedures include elective procedures such as lumbar discectomies, laminectomies, and one- or two-level anterior cervical discectomies/fusions. Complex spinal procedures include instrumented fusion of any type (for trauma, degenerative disease, or deformity correction), laminoplasty, anterior approaches to the thoracic or lumbar spine, and any combined anterior-posterior (360-degree) spinal surgical procedure. Further, with respect to underlying etiologic spinal disorder, patients who have sustained trauma to the spinal column, and particularly those who have an accompanying SCI, are recognized to be at a distinct increased risk of VTE complications, such that they should be uniquely considered in decision making regarding anticoagulant prophylaxis. This group of patients will be discussed separately.

Risk of Venous Thromboembolism Following Spinal Surgery

Before one can make an informed decision about the relative risk-to-benefit ratio underlying prophylactic postoperative anticoagulation for patients undergoing spinal surgery, it is imperative to understand the incidence of deep venous thrombosis (DVT) and pulmonary embolus (PE) without anticoagulation in this patient population. In an attempt to address this question, Cheng and colleagues performed a meta-analysis examining the risk of DVT and PE in the perioperative period for patients who did not receive prophylactic anticoagulation. Specifically, they attempted to define particular high-risk VTE subpopulations stratified according to the type of underlying etiologic spinal condition for which spinal surgical occurred. These authors noted that for patients undergoing elective operations for deformity in three studies, the rate of DVT was 5.3% and the rate of PE was 2.7%; in non-SCI spinal column trauma patients undergoing spinal surgery in two studies, the risk of DVT was 6.0% (it was 18% in one study); in patients undergoing surgery for degenerative conditions in seven studies, the rate of DVT was 2.0%. Fatal PE was reported only twice over the 14 total studies that were analyzed—once in a trauma patient and once in a degenerative disease patient after an anterior lumbar procedure. In summary, Cheng and colleagues concluded that the risk of DVT in elective spine surgery without chemical prophylaxis was 1 to 2% but up to 18% in the trauma population, whereas the risk of fatal PE was extremely low in elective spinal surgery (0.05%) but occurred in 2% of reported spinal surgery for spinal column trauma. It must be emphasized that there were a limited number of studies available for
analysis, and thus low numbers in the different surgical groups significantly weakened the power of the subgroup analysis. Despite the low level of evidence associated with these numbers the apparent increased risk of VTE complications in those patients undergoing surgery for spinal column fractures is compelling. Accordingly, we feel that it is prudent to consider spinal column trauma patients, irrespective of the presence of SCI, as at a distinct increased risk of VTE.

Two additional reviews have attempted to define the prevalence of VTE in spinal surgery.6,7 Sansone et al6 noted a DVT incidence of 1.09% and a PE incidence of 0.06% in a heterogeneous group of patients undergoing elective spine surgery (a subset of whom received DVT prophylaxis). An older literature review by Catrical reported a raw incidence of VTE complications in a heterogeneous group of patients undergoing elective spinal surgery as 7.1%. Catrical noted that the reviewed studies were of poor quality and thus felt that the derived incidence was suspect.

The incidence of PE after major thoracolumbar spine surgery (posterior fusion, anterior fusion, combined procedures (anterior and posterior) in patients treated with elastic antiembolism stockings and sequential compression devices until ambulatory (but no chemoprophylaxis) was found to be 2.2% in another study.8 A combined anterior-posterior approach was noted to have a statistically significant higher incidence of PE (6.0%) than in patients undergoing posterior procedure alone (p < 0.01).8 Boakye et al9 used the National Inpatient Sample to study complications of 58,115 patients (with variable prophylaxis) undergoing spinal surgery for cervical spondylotic myelopathy. Findings included higher VTE in patients undergoing fusion for cervical spondylotic myelopathy (0.73%) versus fusion for cervical spondylotic myelopathy alone (0.25%). Moreover, in patients undergoing fusion for cervical spondylotic myelopathy, posterior fusion had a higher rate of DVT/PE (1.38%) when compared with anterior fusion (0.60%). Other traditional VTE risk factors such as older age, prior VTE, immobilization, thrombophilia, and malignancy also increase VTE risk in spinal surgery. One retrospective study of more than 35,000 patients undergoing spinal surgery found the VTE risk to be 0.5% (95% confidence interval [CI], 0.4–0.5%) for nonmalignant disease, and 2.0% (95% CI, 1.4–2.6%) for malignant disease.10

To summarize, although the available studies are largely of poor quality, it is readily apparent that while there is a low (but nonnegligible) incidence of VTE complications in spinal surgery patients as a whole, there are distinct subgroups of spinal surgery patients (e.g., spinal column trauma, deformity correction, combined anterior-posterior surgical approach, and individuals with malignant disease) subjected to significant increased VTE risk.

Risk of Perioperative Spinal Hemorrhage in Patients Undergoing Spinal Surgery

Following the identification of particular spinal surgery groups at particular risk of VTE complications, one must also consider the risk of bleeding complications in the postoperative spinal surgery patient population before one can safely administer anticoagulant prophylaxis to ameliorate VTE risks. In particular, it is important to recognize subgroups of patients who are at higher risk of bleeding complications either to adjust therapy accordingly, or to provide closer surveillance and earlier investigation of potential bleeding complications. To this end, there have been two retrospective studies examining both the incidence and predisposing risk factors for spinal hemorrhage following spinal surgery.15,16 Kou et al16 found
12 incidences of SEH in 12,000 spinal procedures (giving an incidence of 0.1%). Similarly, Awad et al\textsuperscript{15} found 32 incidences of SEH in nearly 15,000 operations (incidence of 0.2%). This incidence is consistent with previously reported estimates as reviewed by Aono and colleagues.\textsuperscript{17} Awad et al further identified significant risk factors for postoperative SEH as age > 60, more than five 5 operative levels, intraoperative blood loss > 1 L, international normalized ratio (INR) > 2.0 in the first 48 hours postoperatively, and recent preoperative nonsteroidal anti-inflammatory drug (NSAID) use (although the exact timing was unspecified).\textsuperscript{15} Kou et al identified multilevel procedures (likelihood ratio [LR = 12.42] and coagulopathy (LR = 38.78) as having statistically significant higher risk for developing postoperative SEH.\textsuperscript{16} Factors analyzed in these studies\textsuperscript{15,16} but not found to significantly affect the incidence of SEH were the use of drains, intraoperative durotomy, body mass index (BMI), smoking, and well-controlled anticoagulation for DVT or cardiovascular prophylaxis (though the exact regimens were not specifically delineated).

Intuitively, intraoperative drain insertion should lower the risk of SEH as excess blood is evacuated; however, the findings of these retrospective studies\textsuperscript{15,16} agree with the only prospective study examining this topic,\textsuperscript{18} which did not show any benefit of drain insertion in terms prevention of SEH, mortality, or infection rate in patients undergoing single level laminectomy.

Most recently, a 2011 study examined the incidence of symptomatic SEH in over 6,000 patients undergoing spine surgery and found an overall incidence of 0.41%.\textsuperscript{17} Aono and colleagues\textsuperscript{17} further examined the incidence of SEH among different types of spinal surgical procedures and noted the following incidences: 0% (none of 1,568) in standard lumbar diskectomy, 0.50% (eight of 1,614) in lumbar laminectomy, 0.67% (eight of 1,191) in posterior lumbar interbody fusion (PLIF), 4.46% (five of 112) in thoracic laminectomy, 0.44% (four of 910) in cervical laminoplasty, and 0.21% (1 of 466) in anterior cervical decompression and fusion. Thus, although thoracic laminectomy appeared to be associated with an increased incidence of symptomatic SEH, likely related to the small thoracic spinal canal diameter relative to the cervical and lumbar spines (even following laminectomy), there was no observed increased SEH risk between “simple” spinal procedures such as lumbar laminectomy and “complex” procedures such as PLIF.\textsuperscript{17}

### Postoperative Venous Thromboembolic Prophylaxis for Spinal Surgery

There are very few randomized trials comparing the efficacy of prophylactic VTE strategies in spinal surgery patients. Those trials that do exist are limited by small sample size and the difficulties in detection of asymptomatic DVT.\textsuperscript{19} A meta-analysis including these trials as well as other neurosurgical trials (many of which also included a subset of spinal surgery patients) has also examined this topic.\textsuperscript{25} Clinical guidelines reported by Gould et al\textsuperscript{19} in 2012 suggest inferring treatment decisions based on this pooled analysis.\textsuperscript{25} This large mixed meta-analysis (7779 patients in 18 randomized trials and 12 cohort studies were included) offers an accurate picture of prophylactic intervention efficacy but is confounded by the presence of cranial neurosurgical patients. The authors found a 59% reduction in DVT (relative risk [RR], 0.41; 95% CI, 0.21–0.78) when using intermittent pneumatic compression (IPC) devices. The reduction in PE was not significant with IPCs. Also, there was a 40% relative risk reduction in DVT when comparing low molecular weight heparin (LMWH) versus compression stocking (RR, 0.60; 95% CI, 0.44–0.81).
Other pooled analyses based on comparative prophylactic regimes did not show any significant difference between IPC versus compression stockings, LMWH versus IPC, LMWH versus unfractionated heparin (UFH), and UFH versus placebo.

Further, the pooled neurosurgical data showed no significant increased risk in major hemorrhage when using heparin compared with mechanical methods. However, there was a trend toward increased risk of minor hemorrhage with LMWH compared with mechanical prophylaxis alone (RR, 2.06; 95% CI, 0.18–5.09). Interestingly, a small prospective trial using only IPC devices found only one DVT/PE in 100 consecutive patients undergoing single-level anterior corpectomy/fusion.

**Timing of Venous Thromboembolic Chemoprophylaxis Initiation for Patients Undergoing Spinal Surgery**

There is a single retrospective cohort study that analyzed preoperative VTE chemoprophylaxis with respect to the incidence of postoperative DVT/PE and SEH. The authors concluded that although preoperative prophylaxis with UFH or LMWH did not significantly increase the risk of postoperative SEH, it also did not reduce the incidence of postoperative VTE complications.

Is early postoperative DVT prophylaxis with LMWH associated with an increased risk of hemorrhage? Gerlach et al retrospectively evaluated 1,954 patients undergoing a wide range of spine surgical procedures and in whom early (< 24 hours postoperative) subcutaneous LMWH prophylaxis was administered, and noted a SEH rate of 0.4%. Thus, it appears that early LMWH prophylaxis is not associated with an increased risk of hemorrhage postoperatively and, accordingly, is safe to start within 24 hours of surgery. This is in agreement with the mixed neurosurgical meta-analysis that did not show a difference in major hemorrhage rate when the first dose of prophylactic heparin was administered preoperatively, intraoperatively, or postoperatively. Accordingly, as is reflected in Gould et al’s 2012 guidelines, it does appear that preoperative or early postoperative chemoprophylaxis is safe in patients who are at high risk of perioperative VTE complications.

**Recommendations for Venous Thromboembolism Prophylaxis in Spinal Surgery Patients Without Spinal Column or Spinal Cord Injury**

Based on the pooled analysis of Collen et al. in combination with identification of particular subgroups of nontrauma spinal surgery patients at higher risk of VTE complications, Gould et al’s 2012 clinical guidelines make the following specific recommendations for VTE prophylaxis for patients without traumatic spinal column or cord injuries undergoing spinal surgery:

- For patients undergoing spinal surgery, mechanical prophylaxis, preferably with IPC, is recommended. There is no compelling evidence to recommend UFH or LMWH.
- For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease and those undergoing surgery with an anterior or combined anterior-posterior approach), we suggest adding pharmacological prophylaxis (UFH or LMWH) to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases.
Risk of Venous Thromboembolism in Spinal Surgery Patients with Traumatic Injury to the Spinal Column or Spinal Cord

Although traumatic injuries are heterogeneous in nature, they are universally associated with a high risk of VTE. Indeed, a review of the incidence of VTE complications in trauma patients noted a range from 5 to 63%, dependent on the specific type of traumatic injury, modality of prophylaxis, and the particular method of detection employed. Despite this tangible risk of VTE complications, decision making regarding prophylaxis in trauma patients remains challenging due to the potentially calamitous consequences of bleeding complications in the trauma population, particularly in cases of visceral, spinal, and head injury.

Numerous studies have found that spinal column fractures and SCI are potent risk factors for the development of VTE complications. This is reflected in their inclusion as individual risk factors in the VTE risk assessment profile (RAP) developed by Greenfield et al. As has been discussed previously, Cheng et al. noted a 6% risk of DVT in non-SCI spinal trauma patients not receiving prophylaxis, which was higher than any other subset of spinal surgery patients. Even in the face of various prophylactic regimens VTE risks remain high for non-SCI spinal trauma patients, with a pooled incidence of 2.2%. A systematic review by Velmahos et al. further noted that patients with spinal fractures had an odds ratio of 2.3 for VTE in comparison to other patients with trauma, a cohort that already has a recognized elevated risk.

Despite the elevated risk of VTE in spinal trauma patients, individuals with SCI represent the cohort of either spinal surgery patients or trauma patients at the highest risk of VTE complications. It is estimated that 67 to 100% of patients with acute SCI will develop VTE (symptomatic or asymptomatic) in the first 3 months following their injury. VTE is a significant cause of morbidity and mortality in SCI patients and is responsible for 9.7% of all deaths in the first year following acute SCI. Given the marked elevation of VTE risk, it is widely recognized the prophylactic regimens must be considered in the spinal trauma and SCI patient populations.

Risk of Perioperative Spinal Hemorrhage in Spinal Surgery Patients with Traumatic Injury to the Spinal Column or Spinal Cord

Very few studies have examined the bleeding complications associated with spinal column or spinal cord injury. To date, only three trials in patients with trauma reported bleeding complications in patients who did not receive chemical VTE prophylaxis. In those trials, the pooled risk of bleeding complication was 0.7%, a number that likely represents the lower baseline bleeding risk in the trauma population.

Similarly, few studies have examined the bleeding complications of spinal column or SCI patients associated with VTE chemical prophylaxis. Christie et al., in their review, noted a low rate of bleeding complications among SCI patients receiving VTE prophylaxis, ranging from 0 to 2.6% in a limited number of available studies. Boakye et al., in a 2008 National Inpatient Sample (NIS) study, retrospectively examined over 31,000 SCI patients with the goal of evaluating outcomes and
complications, stratified according to the level of SCI and management (nonoperative versus laminectomy alone versus laminectomy and fusion). Though not explicitly stated, it is assumed that these patients were treated with some variety of VTE prophylactic strategy for an appropriate duration. DVT/PE occurred in 1.4% of nonoperative cases, 2.64% of laminectomy alone cases, and 2.46% in laminectomy and fusion cases. Postoperative hematoma occurred in 3.37% of laminectomy alone and 3.82% of laminectomy and fusion. Interestingly, postinjury hematoma was also reported in 0.84% of patients undergoing nonoperative management. These estimates are similar to the 1% incidence of symptomatic SEH in patients suffering spinal trauma that was quoted in a previous study. In this particular study, T7-T12 injuries had the highest incidence of postoperative hematoma at 4.78%, whereas non–fracture-associated SCI at that same levels had the lowest incidence at 1.5%. For operatively managed patients, the incidence of DVT/PE was lowest with nonfracture SCI at the level of T1-T6 (0%) and highest among fracture-related injuries at the same levels (4.71%). For nonoperatively managed patients, the incidence of DVT/PE was lowest with nonfracture cord injuries at the level of T7–12 (0.98%) and highest among fracture-related injuries at T1-T6 (3.3%). Overall, there was a trend toward lower incidences of DVT/PE and postoperative hemorrhage with cord injuries secondary to non–fracture-related mechanisms than those with fracture-related mechanisms.

Venous Thromboembolic Prophylaxis for Patients with Traumatic Injury to the Spinal Column or Spinal Cord

Given the high rate of VTE in these patient populations, combined with the apparent low rate of major bleeding complications, the literature supports the routine use of VTE prophylaxis for patients with spinal column or spinal cord traumatic injury. Of course, it must be recognized that there are commonly accepted relative contraindications to the use of chemical thromboprophylaxis that include severe head injury, nonoperatively managed liver or splenic injuries, renal failure, SCI associated with epidural hematoma, severe thrombocytopenia, and coagulopathy. Teasell et al conducted a large systematic review and meta-analysis of VTE prophylaxis in SCI patients, specifically examining chemical prophylaxis, mechanical VTE prophylaxis, and combination methods. They analyzed 23 separate studies that met their predefined inclusion criteria, including 13 studies that examined VTE chemical prophylaxis in SCI patients. Ultimately, they were able to reach several conclusions regarding thromboprophylaxis in SCI patients. First, they concluded that prophylaxis with UFH of 5000 IU twice daily is not superior to placebo alone in preventing DVT post-SCI, based on the combined findings of one small randomized controlled trial (RCT) and one nonrandomized trial. They further noted, on the basis of a single RCT, that dose-adjusted UFH appeared superior to standard (5000 IU) twice daily dosing in the prevention of DVT (31% to 7%) but had a significantly higher risk of bleeding complications (0 vs 7%). Teasell et al also concluded that LMWH is superior to standard dose UFH in preventing VTE and has a lower rate of bleeding complications, based on two RCTs and two nonrandomized trials. The LMWH used in the majority of patients in these trails was enoxaparin. This conclusion is slightly different from that reached in a meta-analysis by Ploumis et al, who noted a similar odds ratio following thromboprophylaxis with UFH versus LMWH (2.8 and 2.7, respectively) for the development of PE. However,
they state that UFH is significantly associated with increased bleeding risk compared with LMWH, though other heparin-related complications were not different between the two.

Other studies have attempted to determine whether there was superiority of a particular LMWH for VTE prophylaxis in the setting of SCI. One randomized trial of 129 patients determined that 30 mg of enoxaparin administered twice daily via a subcutaneous route showed no differences in VTE rates or bleeding complications in comparison with 40 mg of subcutaneous enoxaparin administered once daily. Similarly, Chiou-Tan et al, in a randomized trial of 95 patients, noted no difference in either VTE or bleeding complications between dalteparin 5000 IU subcutaneously once daily versus enoxaparin 30 mg subcutaneously twice daily.

In addition to chemical VTE prophylaxis, mechanical prophylaxis has also been examined in SCI patients by Winemiller et al. Based on this case series with multivariate analysis, there is limited evidence that IPC or a gradient elastic stocking (GES) independently decrease the risk of DVT/PE. Interestingly, there is no high-quality evidence that chemical VTE prophylaxis combined with mechanical compression devices is superior to mechanical compression alone for acute SCI patients, although this scenario has been poorly studied. However, in deference to the conclusion of Winemiller et al, this does at least imply that mechanical compression devices have some efficacy in VTE prevention and, accordingly, in situations where anticoagulation is contraindicated (such as intracranial hemorrhage, hemothorax, and other active bleeding), mechanical VTE prophylaxis should be implemented as soon as feasible. Similarly, as noted by Teasell et al, there is little evidence that combination (i.e., mechanical and chemical) methods are superior to LMWH alone, simply because this particular paradigm has not been studied specifically in the SCI population. However, given the well-established significantly elevated risk of VTE in this patient population, combination VTE prophylaxis would intuitively be at least as effective, if not marginally more effective, in the prevention of VTE with no added bleeding risk. Accordingly, a combination prophylaxis paradigm should be considered in the acute spinal injured population, at least until a high-quality analysis is available to support or refute this practice.

**Timing of Venous Thromboembolic Chemoprophylaxis Initiation for Spinal Surgery Patients with Traumatic Injury to the Spinal Column or Spinal Cord**

Christie et al conducted a systematic review with the goal of determining the ideal timing (i.e., after SCI or after subsequent spinal surgery) for initiation of VTE prophylaxis in the acute SCI patient. They subsequently only identified a single study that was specifically designed to determine the effects of timing of prophylaxis after acute SCI. In this study, Aito and colleagues compared 275 SCI patients divided into either an early VTE prophylaxis group (within 72 hours) or a late group (initiation after 72 hours). All patients received mechanical prophylaxis with IPC or GES, and chemical prophylaxis with LMWH (nadroparin). They noted a substantially lower incidence of DVT, as detected by Doppler ultrasonography, in the early group (2%) as compared with the late group (26%). In this same study, a subgroup analysis noted that American Spinal Injury Association (ASIA) grade A SCI patients were more substantially likely to develop DVT as compared with ASIA grade A SCI patients.
grade D SCI patients (incidence of 36% vs 7%). On the basis of this compelling data, Christie et al recommend early (< 72 hours postinjury) initiation of VTE prophylaxis in the setting of acute SCI.24

In addition, Christie et al also reviewed the use of chemical VTE prophylaxis in the perioperative period for acute SCI patients. Two prospective trials21,22 and one retrospective review23 were identified that addressed this issue. The combined findings of these studies noted a low incidence of major bleeding complications (0–2.6%) and an incidence of PE of 0 to 5.2% and symptomatic DVT of 0 to 1.7% that was not substantially elevated above baseline. Accordingly, based on a balance of risk and with the caveat that any recommendation is supported by weak data, Christie et al ultimately recommended withholding LMWH on the morning of surgery and resuming within 24 hours postsurgery.

Recommendations for Venous Thromboembolism Prophylaxis in Spinal Surgery Patients with Spinal Column or Spinal Cord Injury

The following recommendations for patients with SCI are made by adapting the clinical guidelines for all major trauma patients, including spinal column and cord injuries, of Gould et al,19 in combination with the recommendations of other systematic reviews of VTE prophylaxis in SCI patients24,29:

- The use of UFH, LMWH, or IPC mechanical prophylaxis is suggested over no prophylaxis.
- Chemoprophylaxis should be instituted within 72 hours of injury.
- Low molecular weight heparin should be withheld on the morning of surgery and resumed within 24 hours following surgery.
- For major trauma patients at high risk for VTE, including all patients with acute SCI and requiring spinal surgery for trauma (without or without SCI), combination pharmacological prophylaxis and mechanical prophylaxis is recommended when not contraindicated by lower-extremity injury.
- For major trauma patients, including all patients with acute SCI and requiring spinal surgery for trauma (without or without SCI), in whom LMWH and low-dose unfractionated heparin (LDUH) are contraindicated, mechanical prophylaxis, preferably with IPC, is suggested over no prophylaxis when not contraindicated by lower-extremity injury. Addition of pharmacological prophylaxis should commence when the risk of bleeding diminishes or the contraindication resolves.
- In patients with acute SCI requiring spinal surgery for trauma (without or without SCI) inferior vena cava (IVC) filters should not be used for primary VTE prevention.
KEY POINTS

• The risk of spontaneous spinal hemorrhage is very low in patients with well-controlled anticoagulation therapy, and is likely not statistically more probable to occur than in the general non-anticoagulated population.
• There is no evidence that spinal vascular malformations have an increased risk of hemorrhage following initiation of anticoagulation therapy.
• Although there is a low (but nonnegligible) incidence of VTE complications in spinal surgery patients in general, there are distinct subgroups of spinal surgery patients (e.g., spinal column trauma, deformity correction, combined anterior-posterior surgical approach, and individuals with malignant disease) that are subjected to significant increased VTE risk.
• The risk of symptomatic postoperative spinal epidural hematoma ranges from 0.1 to 0.4% and is associated with more complex surgery, higher intraoperative blood loss, early postoperative elevated INR, and thoracic spinal surgery.
• Spinal cord injury patients have an extremely high incidence of venous thromboembolism, with estimates ranging from 67 to 100% in the first 3 months after SCI.
• Venous thromboembolism is a significant cause of morbidity and mortality in SCI patients and accounts for almost 10% of all deaths in the first year following acute SCI.

REVIEW QUESTIONS

1. Spontaneous spinal hemorrhage occurs most frequently in which anatomic compartment?
   A. Subdural
   B. Subarachnoid
   C. Epidural
   D. Intramedullary

2. What is the most frequent cause of spontaneous spinal hemorrhage?
   A. Therapeutic anticoagulation
   B. Spinal vascular malformation
   C. Blood dyscrasia
   D. Idiopathic

3. Which of the following subgroups of spinal surgery patients is NOT associated with an elevated risk of perioperative venous thromboembolism?
   A. Lumbar spondylosis
   B. Deformity
   C. Spinal tumor
   D. Spinal column fracture

4. Which spine surgical procedure is associated with the highest incidence of postoperative symptomatic spinal epidural hematoma?
   A. Cervical laminoplasty
   B. Thoracic laminectomy
   C. Transforaminal lumbar interbody fusion
   D. Anterior cervical decompression and fusion
5. Regarding the timing of initiation of chemoprophylaxis in patients undergoing spinal surgery, which of the following statements is correct?

A. Preoperative chemoprophylaxis did not increase the risk of postoperative hematoma or reduce the incidence of postoperative VTE complications in comparison with postoperative chemoprophylaxis.

B. Preoperative chemoprophylaxis increased the risk of postoperative hematoma but reduced the incidence of postoperative VTE complications in comparison with postoperative chemoprophylaxis.

C. Preoperative chemoprophylaxis increased the risk of postoperative hematoma and increased the incidence of postoperative VTE complications in comparison with postoperative chemoprophylaxis.

D. Preoperative chemoprophylaxis decreased the risk of postoperative hematoma and decreased the incidence of postoperative VTE complications in comparison with postoperative chemoprophylaxis.

6. Regarding VTE prophylaxis in SCI patients which of the following statements is NOT correct?

A. LMWH is the chemoprophylaxis of choice.

B. Combination chemoprophylaxis and mechanical prophylaxis should be routinely employed.

C. IVC filters should be routinely administered.

D. Chemoprophylaxis should commence within 72 hours of injury.

References


**ANSWER KEY**

1. C
2. D
3. A
4. B
5. A
6. C
Both intraoperative hemostasis and coagulation management as well as postoperative venous thromboembolism (VTE) prophylaxis are crucial aspects of appropriate spine surgical care. Modern spine surgical care involves the treatment of a wide array of pathologies across a substantial breadth of surgical case complexity and, accordingly, the particular nuances of hemostasis and coagulation also vary widely in parallel with underlying etiology and degree of complexity of surgical intervention. Specific case examples are presented here to illustrate several aspects of hemostasis and anticoagulation as they relate to the care of the spine surgery patient.

**Case 1: Spinal Stenosis**

**History**

A 67-year-old man with a medical history of hypertension and diabetes presented with an 18-month history of progressive ambulatory dependent bilateral leg pain radiating to his lower legs. Severe pain was brought on by walking less than one city block and relieved completely with sitting or forward flexion. Physical examination identified a normal neurologic examination and normal pedal pulses. A recent magnetic resonance imaging (MRI) study showed evidence of severe central and lateral recess spinal stenosis at the L3/4 and L4/5 secondary to a combination of facet arthropathy and ligamentum flavum hypertrophy. Given the compelling clinical history and excellent radiographic correlation, a diagnosis of neurogenic claudication secondary to lumbar spinal stenosis was entertained, and the option of a minimally invasive lumbar decompression directed at the L3/4 and L4/5 spinal levels was discussed with the patient.

**Procedure**

An uneventful minimally invasive multilevel lumbar decompression was performed. The patient was positioned prone on a Jackson spinal table (OSI, Union City, CA). Intermittent pneumatic compression (IPC) was instituted preoperatively. Operative blood loss was 75 mL. Postoperatively, IPC was continued, and early ambulation was encouraged. No chemical prophylaxis was instituted. The patient tolerated the procedure well and was discharged the following morning.
Discussion

Simple spine surgical procedures such as diskectomies, laminectomies, and one- or two-level fusion operations do not routinely involve significant blood volume loss and, accordingly, perioperative hemostasis is often not a significant issue. However, regardless of the degree of anticipated spine surgical intervention, proper patient positioning remains important to the overall goal of minimizing operative blood and promoting effective hemostasis. The Jackson spinal table leaves the patient’s abdomen free in the prone position and therefore decreases inferior vena cava pressure and, as a result, decreases epidural venous plexus filling. Theoretically, this also decreases vertebral venous pressure and thus lowers intraoperative blood loss from decreased bone bleeding.

Intermittent pneumatic compression is instituted perioperatively, as this method has been shown to be as effective as chemical prophylaxis for low-risk spine surgery patients. Patients undergoing simple spine surgery procedures typically ambulate in the early postoperative phase, and thus do not require chemical prophylaxis. Minimally invasive spine surgery techniques have further reduced the degree of postoperative pain typically experienced by patients, allowing for even earlier ambulation and the transition of many simple spine surgery operations to day-surgery procedures. Chemical prophylaxis is only recommended in this patient population if there are other factors that raise the risk of VTE (e.g., previous VTE, malignancy, prolonged recumbency due to perioperative medical complication).

Case 2: Spinal Deformity (Fixed Sagittal Imbalance)

History

A 61-year-old man presented with a multi-month history of severe, progressive ambulatory leg pain radiating to his bilateral calves. This claudicant leg pain was occurring on the background of long-standing worsening chronic mechanical low back pain and a progressive inability to stand in an upright, erect fashion. His past medical history was significant for having undergone a T10–L3 anterolateral fusion (Dwyer procedure) for scoliosis 30 years previously and a myocardial infarction 1 year ago that was treated via percutaneous placement of a bare-metal coronary stent and dual antiplatelet therapy with clopidogrel (Plavix) and aspirin.

Physical examination demonstrated a substantial thoracic kyphosis and lumbar hypolordosis. No focal deficits were identified on a neurologic examination. Standing scoliosis X-rays demonstrated his previous T10–L3 Dwyer fusion construct combined with a severe fixed sagittal imbalance measuring 17.5 cm (Fig. 26.1) as well as significant degenerative disk disease at the L4/5 and L5/S1 levels caudal to the previous fusion. Lumbar spine MRI (Fig. 26.2) revealed severe spinal stenosis both centrally and in the lateral recesses at the L4/5 and L5/S1 levels.

Diagnoses of fixed sagittal imbalance and adjacent segment degeneration spinal stenosis were made. After a lengthy discussion with the patient about the pertinent risks and benefits of surgical intervention, a T3–ilium posterior instrumented fusion with multiple thoracic Smith-Petersen osteotomies, a L2 pedicle subtraction osteotomy, as well as L4/5 and L5/S1 transforaminal lumbar interbody fusions was planned as a treatment for the patient’s fixed sagittal imbalance and spinal stenosis.
Fig. 26.1a,b  Standing scoliosis series. (a) Anteroposterior view. (b) Lateral view. The prior anterolateral T10-L3 fusion construct is demonstrated as is the severe sagittal imbalance.

Fig. 26.2  Axial T2-weighted magnetic resonance imaging through the L4/5 spinal level demonstrating severe central and bilateral lateral recess stenosis.
**Procedure**

Prior to proceeding to surgery, a detailed cardiac evaluation was completed. The patient’s cardiologist recommended cessation of clopidogrel 7 days prior to the surgical date but continuation of aspirin. It was recommended that clopidogrel be restarted as soon as possible postoperatively, preferably within 48 hours.

On the day of surgery, the patient was placed on IPC devices immediately before the commencement of surgery and positioned on a Jackson spinal table. Total surgical time was 12 hours and surgical blood loss totaled 2.75 L. Intraoperatively, 4 U of packed red cells were administered to maintain hemoglobin in the 90 to 100 g/L range. Platelet levels and intraoperative coagulation tests remained normal throughout, and, accordingly, no platelets or fresh frozen plasma administration was required. Tranexamic acid (TXA) was administered at the commencement of surgery to a dose of 100 mg/kg, followed by infusion of 10 mg/kg/h for the duration of the procedure. Intraoperative autologous blood salvage methods were not employed. Throughout the procedure, judicious use of electrocautery and meticulous wound packing were employed. Regions of significant epidural venous bleeding and cancellous bone bleeding were controlled with the topical application of Floseal (Baxter Healthcare SA, Zurich, Switzerland), a hemostatic matrix consisting of human thrombin, carried in rounded collagen gelatin granules. The patient tolerated the procedure well and remained hemodynamically stable at all times.

He was transferred to the intensive care unit postoperatively and was extubated the following morning prior to transfer to the spine surgery ward. VTE prophylaxis in the immediate postoperative period consisted of IPC devices. Surgical drain output remained high for the first 2 days postoperatively (450 mL and 300 mL, respectively), and a transfusion with a further 2 U of red blood cells for a hemoglobin of 72 g/L was administered on the second postoperative day.

On the third postoperative day, drain output was markedly decreased and, accordingly, clopidogrel was reinstituted. Further, given the patient’s major surgery and anticipated prolonged convalescence/reduced ambulatory state, chemical VTE prophylaxis consisting of 5000 U subcutaneous unfractionated heparin twice daily was started.

**Discussion**

This complex spine surgery case serves to highlight a number of salient points surrounding issues related to perioperative antiplatelet agent usage, intraoperative fluid management, and resuscitation strategies to minimize the development of dilutional coagulopathy in complex spine surgery cases with substantial blood loss, intraoperative surgical strategies to optimize hemostasis, as well as appropriate postoperative VTE prophylaxis for complex spine surgery interventions.

Antiplatelet therapy is commonplace as prophylaxis for cerebrovascular or coronary thrombosis syndromes. Increasingly, patients are maintained on dual antiplatelet therapy with both aspirin and clopidogrel, particularly following coronary artery stenting to prevent late angiographic stent thrombosis. Clopidogrel is a thienopyridine agent that acts as an inhibitor of adenosine diphosphate–induced platelet aggregation, and accordingly has a very potent antiplatelet effect. In practice, elective complex spine surgery interventions should not be performed in the presence of clopidogrel, as the risk of significant blood loss and postoperative
bleeding complications are substantially elevated. Routinely, antiplatelet agents such as clopidogrel should be stopped 7 days before surgical intervention to allow for reestablishment of normal platelet function. Urgent medical reversal of clopidogrel, if required, is best achieved with platelet transfusion. As in this particular case, complex spine surgery procedures can be performed in the presence of active aspirin therapy if the risk of discontinuation of aspirin is deemed to be quantifiable. In such a scenario, the surgeon should actively monitor intraoperative blood clotting and consider platelet transfusion in the face of mounting blood loss.

Although the timeline for cessation of antiplatelet agents is well established, when to resume such medications after elective surgery is less clear. Typically, it has been recommended that clopidogrel be resumed within 12 to 48 hours postoperatively assuming satisfactory postoperative hemostasis has been achieved. In general, this is reasonable, but it should be noted that there are several case reports of delayed symptomatic epidural hematoma occurring up to 12 days postoperatively in association with clopidogrel therapy. Thus, careful clinical follow-up of spine surgery patients on antiplatelet therapy is recommended.

Patients undergoing major spine surgery are prone to develop coagulopathy because of large-volume replacement for the blood loss and results from the dilutional effect of fluid replacement, the direct impairment of the fibrinogen/fibrin polymerization process, as well as the direct consumption of platelets and clotting factors. In general, for major spine surgery, a higher threshold for administration of blood products (e.g., maintenance of a hemoglobin of 100 g/L) limits the use of crystalloid and thus reduces the potential for development of dilutional coagulopathy. Careful monitoring of platelets, international normalized ratio (INR), and fibrinogen levels are also critical to help guide transfusion therapy during long spine surgery procedures.

Antifibrinolytics such as TXA, aprotinin, and ε-aminocaproic acid have been extensively studied and appear to have a role in reducing intraoperative blood loss and minimizing blood transfusion with no increase in VTE complications. Although there is some evidence to suggest that aprotinin is more effective than TXA in cardiac surgery, no difference in efficacy was noted in orthopedic surgery. A recent meta-analysis of TXA in spine surgery further concluded that it was safe and effective and reduced blood loss and the need for transfusion, particularly if administered at doses above 15mg/kg. At our institution, a TXA bolus followed by infusion is the routine for complex spine surgery operative cases.

Intraoperative autologous blood salvage using devices such as the Cell Saver (Haemonetica, Braintree, MA) can also be considered for complex spine surgery procedures and can help to reduce the need for allogeneic blood transfusion. Blood loss on the surgical field is collected through a suction, then filtered, anticoagulated, washed, and reinfused to the patient. This procedure has a well-established safety profile and does appear to be cost-effective for procedures with greater than 500 mL of blood loss. However, other studies have suggested that when intraoperative blood loss is greater than 1000 mL, as is the case for many complex spine surgery procedures, the chance of receiving allogeneic blood is significantly increased regardless of the use of a Cell Saver and accordingly renders it ineffective.

In complex spine surgery cases VTE prophylaxis options must also be carefully considered, given the duration of surgery and the typical prolonged postoperative period of substantially reduced ambulation. Routine use of IPC devices from the onset of surgery is recommended. Once adequate surgical hemostasis is obtained, chemical VTE prophylaxis with either unfractionated heparin or low molecular weight heparin is recommended until hospital discharge.
Case 3: Acute Spinal Cord Injury

History

A 28-year-old man was involved in a high-speed dirt biking accident in which he fell 30 feet into a mountain ravine. He reported being immediately unable to move or feel his arms or legs and complained of severe neck pain. On examination in the emergency room he was noted to have a blood pressure of 85/35 mm Hg, a heart rate of 47, and no other systemic injuries. Neurologic examination revealed an American Spinal Injury Association (ASIA) grade A C5 spinal cord injury. A plain cervical radiograph (Fig. 26.3) revealed gross malalignment of the cervical spine and a cervical spine CT scan (Fig. 26.4) confirmed a bilateral C6/7 facet fracture-dislocation.

Procedure

Given the patient’s acute, complete cervical spinal cord injury, he was taken urgently to the operating room for an open reduction and combined anterior-posterior C5-7 instrumented fusion (Fig. 26.5). The operation occurred in an uneventful fashion, but the patient did not show any signs of return of neurologic function and remained an ASIA grade A C5 tetraplegic. Chemical VTE prophylaxis with low molecular weight heparin (enoxaparin) was instituted on the first postoperative day and continued long-term.

Fig. 26.3 Cervical spine radiograph demonstrating gross spinal malalignment at the C6/7 level.
Discussion

Many of the nuances of intraoperative hemostasis that were discussed in the previous complex spine surgery case also apply here. This case highlights the necessity to commence early chemical VTE prophylaxis with a low molecular weight heparin, as the preferable method or unfractionated heparin or mechanical prophylaxis alone. The duration of prophylaxis remains uncertain, but there is a developing consensus that it should be continued indefinitely as long as no contraindications to its ongoing use develop.

Fig. 26.4a–c  Cervical spine computed tomography reveals a bilateral facet fracture dislocation and spondyloptosis at the C6/7 level. (a) Left parasagittal image. (b) Mid-sagittal image. (c) Right parasagittal image.

Fig. 26.5  Postoperative cervical radiograph revealing a circumferential decompression and fusion of C5–7.
References


The balance between prevention of thrombotic phenomena and hemorrhagic complications in the neurosurgical patient population presents an ongoing clinical dilemma. The risk of specific procedures, in the context of patient comorbidities and the associated treatments with antiplatelet and anticoagulant therapy, produces a complex decision tree with many permutations. Frequently there exists no solid, evidence-based guidelines on which to frame these decisions and help maximize the risk–benefit profile for a given intervention. This chapter examines the role of anticoagulant and antiplatelet agents in the context of cerebrospinal fluid (CSF) shunts, external ventricular drains, intracranial pressure monitors, and lumbar drains.

There can be substantial variability in treatment paradigms based on institutional protocols as well as surgeon preference. There is a paucity of studies with respect to these specific neurosurgical procedures in the context of antiplatelet and anticoagulant therapy. The treatment plan for patients with brain and spinal catheters who experience hemorrhagic complications is often dictated by their clinical status, the predicted clinical course, and a perceived optimal risk–benefit profile. This chapter highlights some of the clinical issues pertinent to these procedures as well as our own clinical practice-based experience and institutional guidelines. There are ongoing studies specifically addressing some of these clinical dilemmas, but there is a need for further investigation and prospective data collection to determine the optimal guidelines and protocols.

Cerebrospinal Fluid Shunts

Cerebrospinal fluid shunting as a procedure has been practiced since the 1950s. The patient population that receives these devices is primarily pediatric because hydrocephalus is the primary indication for their placement. However, since the mid-1960s, shunts have been used to treat the diagnosis of normal pressure hydrocephalus (NPH). NPH primarily affects patients in the elderly population and therefore has relevance in understanding procedure-associated complications from the use of anticoagulant and antiplatelet agents.

Complications from shunt placement in all age groups include infection, malfunction, seizures, subdural hematoma, and, rarely, intracerebral hemorrhage. Patients with NPH represent a specific subpopulation that receives shunts, and patients with NPH who are on antiplatelet or anticoagulation therapy, primarily for age-related cardiovascular disease, represent a significant proportion of this group. There have been relatively few investigations that have looked at the hemorrhagic
complication rates in patients undergoing ventriculoperitoneal (VP) shunt in the context of these agents.

The occurrence of intracranial ventricular catheter-related hemorrhage is so rare that it is limited to a handful of case reports in the literature, but it is likely an underreported complication of this procedure. In our experience 1% of patients demonstrate a significant hemorrhage along the catheter tract on immediate postoperative computed tomography (CT) or magnetic resonance imaging (MRI) scans; however, these hemorrhages are rarely symptomatic.

In addition to routine laboratory testing, it is critically important to obtain an appropriate history with respect to any potential bleeding disorder, including a family history of abnormal bleeding. This can help identify and screen for any potentially high-risk patients prone to hemorrhagic complications and help predict the ability to achieve adequate intraoperative hemostasis.

Because shunts are uncommonly placed on an emergent or even urgent basis, placing them can usually be considered an elective procedure. Patients who are on anticoagulants or antiplatelet agents, therefore, should have an appropriate preoperative medical evaluation and risk stratification. There are no specific evidence-based guidelines to determine perioperative management of patients on anticoagulant and antiplatelet therapy, and many institutions create policies and protocols based on studies that may not be specific or even relevant for a neurosurgical patient.

With the lack of specific guidelines for shunt surgery, our institution’s policies have been put into practice based on the most current recommendations and input from medicine, cardiology, anesthesia, and neurosurgery services. In general, patients who are on aspirin are directed to stop therapy 7 days prior to the initial shunt placement. Patients on clopidogrel stop therapy 7 days prior to initial surgery. Patients on oral anticoagulant therapy (Coumadin) discontinue medication 5 days prior to surgery; a preoperative coagulation profile must document a normal international normalized ratio (INR) prior to proceeding to the operating room. If the patient’s risk profile for cardiovascular events is high, the patient can be bridged off of the oral anticoagulant with low molecular weight heparin (LMWH) and can receive the final dose up to 24 hours preprocedure.

Shunt malfunction is an unfortunate but rather common complication in patients of all ages including those with NPH. In the NPH population, most commonly the malfunction is distal (intra-abdominal) obstruction, and revision surgery for these patients is usually limited to intra-abdominal exploration and repositioning of the distal catheter. Because there is no intracranial catheter manipulation for this procedure, patients are not routinely asked to stop aspirin, with the understanding that there is a small, but increased, possibility of an abdominal wound hematoma. Oral anticoagulants are discontinued as with primary shunt placement.

After a shunt surgery is performed, determining when it is safe to resume anticoagulation or antiplatelet therapy can be more variable. Factors specific to the surgery, postoperative clinical status, and preprocedural risk stratification are taken into consideration. Most often, antiplatelet drugs and anticoagulants will be restarted 5 to 7 days after surgery. However, certain high-risk patients are restarted on antiplatelet agents on postoperative day 2 or 3, and anticoagulants can be restarted on day 3 without using an LMWH bridge while following daily coagulation profiles. A postoperative CT or MRI scan should be obtained prior to resumption of antiplatelet or anticoagulant therapy to document that there is no significant intracranial hemorrhage.

During the perioperative period, the use of routine pharmacological deep venous thrombosis (DVT) prophylaxis is also recommended. The guidelines are gen-
erally similar for patients undergoing other intracranial procedures. Patients are given prophylactic doses of LMWH daily while admitted. This is stopped 24 hours preprocedure and restarted 24 hours postprocedure, provided that there are no concerns about hemorrhagic complications. In addition to pharmacological DVT prophylaxis, sequential compression devices on the lower extremities are ordered for all patients. Early mobilization and ambulation, when the patient is ready, are also important adjuncts to prevention of DVT and pulmonary embolism (PE) in patients undergoing shunts.

Another common and unfortunate complication of shunted NPH is the development of a subdural hematoma. Very few studies have specifically addressed the risks of a subdural hematoma in shunted patients on antiplatelet or anticoagulant therapy. It is thought that overdrainage and abrupt changes in CSF dynamics can precipitate a subdural hematoma. There are some data to suggest that the use of a programmable valve or flow-regulated valves may lower this risk of a subdural hematoma; however, this has not been confirmed in prospective randomized studies. Some patients may initially present with chronic subdural hygromas and expanded extra-axial spaces. Again, a prudent decision may be to use a valve that limits siphoning, including fixed pressure, flow regulated, or programmable devices for these patients to avoid overdrainage and the expansion of the subdural space, which could increase the risk of precipitating a subdural hematoma.

Patients are monitored closely in the postoperative period, both clinically and radiographically, as needed. There is some evidence specific to NPH patients on warfarin therapy that there is no increased risk of a subdural hematoma in the postoperative period. Additionally, patients whose warfarin was discontinued in the perioperative period and whose coagulation profile is normalized do not necessarily experience an increased risk of thromboembolic complications. The few studies that have investigated these dilemmas are limited in their design but demonstrate the importance of further investigations in this area.

External Ventricular Drains and Intracranial Pressure Monitors

The use of external ventricular drains (EVDs) and intracranial pressure (ICP) monitors is common and varies widely in the patient populations and the conditions that they treat. It is an important diagnostic and therapeutic tool in many neurological disease processes. There are many causes of acute hydrocephalus in the neurosurgical patient population including acute aneurysmal subarachnoid hemorrhage, traumatic brain injury, intracerebral and intraventricular hemorrhage, postoperative hydrocephalus, and postoperative CSF leak. These devices are commonly placed at the bedside in an intensive care unit (ICU) or emergency room setting. The specific pathology for which these devices are used commonly presents in patients who are currently on antiplatelet or anticoagulant therapy. There is utility in understanding the hemorrhagic complications associated with these devices for patients who are taking antiplatelet or anticoagulant therapy, but again, little has been written or studied in this context.

As with any procedure, there is an inherent risk of hemorrhagic complication in placing an EVD or ICP monitor. This risk has been studied retrospectively and is estimated to range from 1 to 8%. Although most radiographically evident hemorrhages are not clinically significant, up to 2% can be symptomatic. No study has addressed the risks specific to all patients on antiplatelet or anticoagulant therapy.
However, patients with aneurysmal subarachnoid hemorrhage, requiring EVD placement, have yielded some interesting information and insight into understanding the risks to patients who are on therapy. Patients with acute aneurysmal subarachnoid hemorrhage frequently require placement of a bedside EVD for the development of acute communicating hydrocephalus. With today’s modern endovascular techniques, more patients are receiving definitive treatment of the offending aneurysm using coil embolization or stent-assisted coil embolization. Patients for whom a stent-assisted technique is utilized must be administered aspirin and clopidogrel perioperatively to prevent the high risk of stent-associated thrombotic complications. Kung et al. found that the rates of radiographic hemorrhage from EVD in the stent-assisted patient group were as high as 32%. There was an 8% risk of symptomatic and clinically significant hemorrhage for these patients. The comparison group of patients receiving only coil embolization, and therefore not requiring aspirin and clopidogrel, had a symptomatic hemorrhage rate of only 0.9%. For patients who are on antiplatelet or anticoagulant therapy and present with intraparenchymal or intraventricular hemorrhage, there often exists a need for acute CSF diversion or determination of ICP parameters to optimize best medical management of an otherwise catastrophic intracranial process. Again, there are no guidelines based on level 1 evidence, but it is generally prudent to discontinue the use of these agents, and in most cases reverse these agents prior to placement of an EVD or ICP monitor. Our institutional policy suggests that patients on antiplatelet agents be transfused with platelet products, and patients on anticoagulant therapy should be actively reversed with factors or fresh frozen plasma and vitamin K prior to the procedure. Specific details of reversal agents and their pharmacological details are presented in Chapter 14. Patients should have repeated laboratory testing prior to the procedure to ensure efficacy of the reversal and adequate platelet function and coagulation cascade. When clinical deterioration in a critically ill patient poses time constraints on the reversal process, a risk–benefit analysis should be performed, and a discussion with the patient’s family can help direct appropriate care.

A common complication in patients with intraventricular hemorrhage who require placement of an EVD for acute hydrocephalus is clot-related catheter malfunction. Although there are some bedside maneuvers that can be utilized to flush the clot and reestablish catheter patency, often flow cannot be safely reestablished, and one of the catheters or the ventricular or distal tubing obstructs repeatedly. In some cases, a second EVD can be placed contralaterally when the ICP is increasing and no CSF is draining. In less emergent situations, and when ICP is stable, another option that has become more widely accepted involves the use of intrathecal recombinant tissue plasminogen activator (rtPA). A useful protocol involves removal of 6 mL of CSF prior to injection of 1 mg in 1 mL of rtPA reconstituted in preservative-free sterile saline. The rtPA is flushed into the ventricular system with 5 mL of sterile saline, and the EVD is then clamped for 1 hour. During this time, the ICP is continuously monitored. If the ICP increases above 20 mm Hg, then the drain can be opened after all other maneuvers have been attempted to lower the ICP. The rtPA can be injected every 12 hours, and serial head CTs can be obtained to monitor for clot resolution. Although still controversial, there is some evidence that this method may confer benefit to long-term outcomes.

Patients who require placement of EVD or ICP monitor for CSF diversion or diagnosis of malignant intracranial hypertension are often critically ill and neurologically devastated. Such patients are at extremely high risk for development and
propagation of DVT. To date, no specific studies have addressed the safety or efficacy of pharmacological DVT prophylaxis in patients with EVD or ICP monitors. Our routine practice has been to obtain a postprocedure noncontrast head CT. If there is no evidence of acute catheter- or device-associated hemorrhage, patients are started on subcutaneous heparin (SQH) 24 hours after the procedure as routine DVT prophylaxis. Unpublished preliminary data from our own retrospective review suggest that there is no increased risk of EVD or ICP monitor-related hemorrhagic complications for patients on SQH. Again, the use of pneumatic compression devices is an important adjunct in the prevention of DVT in this patient population. For patients who develop DVT or PE and have an EVD or ICP monitor in place, full anticoagulation is not recommended. A risk–benefit analysis can be performed, and in some cases a decision to remove the EVD or ICP monitor in favor of systemic anticoagulation can be made. For patients in whom systemic anticoagulation is not an option, the placement of an inferior vena cava filter may offer important protection from PE.

**Lumbar Drains and Lumbar Puncture**

Lumbar drains (LDs) are used in a variety of clinical situations and are part of everyday clinical practice for most neurosurgery centers. Their utility varies widely, ranging from CSF diversion for postoperative or traumatic CSF leaks, to routine intraoperative placement for intracranial aneurysm surgery and other skull-based approaches. They are often utilized for preoperative workup and assessment of NPH patients. More recently, there has been some evidence supporting the placement of drains in patients undergoing aortic aneurysm stents or open repair procedures to increase postoperative spinal cord perfusion. Despite their wide clinical use, there are few published data regarding the safety of the procedure and of ongoing use in patients on antiplatelet or anticoagulant therapy.

The primary hemorrhage-related risks and potential complications from LD use involve lumbar epidural hematoma and overdrainage or low-pressure phenomena including the risk of developing a subdural hematoma.

Patients who undergo LD placement should be monitored closely for the development of any neurologic changes to suggest an evolving complication. A preprocedure motor and sensory exam should be well documented, and surveillance monitoring performed regularly postprocedure. The advent of CSF collections systems that limit the amount of CSF drainage per unit of time has been important in reducing the chance of overdrainage–related complications including low pressure headaches and subdural hematoma. Despite the increased safety margin, any unexpected change in neurologic status should prompt an appropriate clinical evaluation and radiographic study.

When considering the use of LDs in the context of patients who are on antiplatelet or anticoagulant therapy, several important points should be noted. There is no direct evidence or published data to assess the risk of hemorrhagic complications from pharmacological DVT prophylaxis in patients undergoing CSF diversion with an LD. A risk–benefit analysis can be attempted prior to initiating prophylactic dosing. A patient with severe traumatic brain injury (TBI) undergoing lumbar drainage who is bed bound has a high risk for DVT, whereas a patient who has an LD placed for NPH workup and is encouraged to ambulate and be mobile while hospitalized is at much lower risk. Some NPH protocols for LD placement include subcutaneous heparin administered twice a day, with very low complication rates.
Although not definitive, there are also data from the vascular surgery literature to suggest that even systemic heparinization intraoperatively does not increase the risk of an epidural hematoma or subdural hematoma when an LD is placed.\textsuperscript{15}

For patients who present for elective LD placement, our practice has been to manage antiplatelet and anticoagulation therapy in a manner similar to our protocol for patients who present for elective VP shunt placement. Preprocedure regimens are stopped and normal coagulation profiles documented. After the LD is removed, the patients may be restarted on the preprocedure therapeutic regimen without additional radiographic imaging unless there has been a deterioration in their clinical examination or new symptomatology. For patients who require more urgent placement of an LD, patients on antiplatelet or anticoagulant therapy can be reversed using agents and protocols appropriate for the degree of urgency.

Another common procedure, and similar in technique to the LD, is the lumbar puncture (LP). The LP is one of the most widely utilized bedside procedures in clinical medicine and its indications are plentiful. Its utility as a diagnostic test, as well as a therapeutic intervention, and the low cost and its relative safety and efficacy make it an attractive procedure. There are limited studies looking at the hemorrhagic complications specifically in patients on antiplatelet or anticoagulant therapy. As with the LD, it is important to document a normal coagulation profile and confer competent platelet function prior to performing an LP. Depending on the indication for the procedure, an appropriate reversal of any antiplatelet or anticoagulant therapy can be pursued prior to the procedure. If there is concern that a patient might have inadequate postprocedure hemostasis, the patient should be monitored closely and any change in neurologic status should be worked up. As with the LD, there is a small risk of a lumbar epidural or subdural hematoma. Although the LP is meant for CSF sampling as compared with continuous CSF diversion, a small percentage of patients will continue to drain CSF into the epidural space postprocedure and are therefore at risk for the development of overdrainage phenomena including an intracranial subdural hematoma. A lumbar epidural blood patch may be required for patients who continue to experience post-LP overdrainage symptoms.\textsuperscript{16}

Other Considerations

The use of indwelling brain and spinal catheters is not limited to CSF shunts, EVDs, ICP monitors, and LDs. There are many variations on a theme, including, depth electrodes for deep brain stimulation, subdural electrodes for seizure surveillance and isolation of seizure focus, and intracranial and lumbar intrathecal drug delivery devices, to name a few. As with the aforementioned brain and spinal catheters, there are even fewer studies examining the role of hemorrhagic complications for patients with these indwelling devices. As the use of antiplatelet and anticoagulant agents will inevitably continue to increase, it will be important to define the role of these agents in the context of the wide variety of implants and devices that are utilized in the field of neurosurgery.

Although avoidance of all hemorrhagic complications in patients undergoing placement of brain and spinal implants is impractical, a thorough understanding of patients' coagulation status and appropriate and thoughtful perioperative management of antiplatelet and anticoagulant therapies can help minimize risk. Balancing the prevention of hemorrhagic complications and thromboembolic events
relies on thorough risk stratification and the judicious timing and use of pharmacological agents in the perioperative period. Close monitoring of clinical status can help identify complications early and direct care in an appropriate manner. Prospective data collection will be an important factor in characterizing the true risks for these given interventions and developing appropriate protocol driven guidelines for the future.

**KEY POINTS**

- Routine pharmacological DVT prophylaxis, both pre- and postprocedure, has a favorable risk–benefit profile in the context of internalized CSF shunts, external ventricular drains, ICP monitors, and LDs.
- Early mobilization when possible and pneumatic compression devices should not be overlooked as important factors in the prevention of DVT and PE in this patient population.
- For elective CSF diversion procedures (shunts and LD trials), preprocedure risk assessment for patients on antiplatelet or anticoagulant therapies should be performed routinely prior to discontinuing any medication.
- The timing for resuming such therapies postprocedure should be based on preprocedure risk stratification and any patient-specific clinical considerations.
- In emergency situations, patients on antiplatelet or anticoagulant therapy should be appropriately reversed and a normalized coagulation profile documented prior to placement of ventriculostomy, ICP monitor, or LD.

**REVIEW QUESTIONS**

1. Regarding the insertion of a ventricular catheter for a VP shunt, are the following statements true or false?
   A. 5% of patients will have a symptomatic ventricular catheter tract hemorrhage.
   B. 1% of patients will have a symptomatic ventricular catheter tract hemorrhage.
   C. 5% of patients will have an asymptomatic ventricular catheter tract hemorrhage.
   D. 1% of patients will have an asymptomatic ventricular catheter tract hemorrhage.
   E. Symptomatic ventricular catheter tract hemorrhages are rare.

2. Regarding the planning of elective VP shunt surgery, are the following statements true or false?
   A. Aspirin should be stopped for 7 days before surgery.
   B. Clopidogrel should be stopped for 3 days before surgery.
   C. Unfractionated heparin should be stopped for 6 hours before surgery.
   D. LMWH should be stopped for 24 hours before surgery.
   E. Dabigatran should be stopped for 1 day before surgery.
3. Regarding the insertion of an external ventricular drain or ICP monitor, are the following statements true or false?
   A. Up to 8% of patients will have a symptomatic ventricular catheter tract hemorrhage.
   B. 2% of patients will have a symptomatic ventricular catheter tract hemorrhage.
   C. Up to 8% of patients will have an asymptomatic ventricular catheter tract hemorrhage.
   D. 2% of patients will have an asymptomatic ventricular catheter tract hemorrhage.
   E. Symptomatic ventricular catheter track hemorrhages are rare.

4. Regarding the emergency insertion of an external ventricular drain or ICP monitor, are the following statements true or false?
   A. Aspirin does not significantly increase the risk of symptomatic or asymptomatic hemorrhage in this situation.
   B. Clopidogrel does not significantly increase the risk of symptomatic or asymptomatic hemorrhage in this situation.
   C. The risk of asymptomatic hemorrhage in patients taking aspirin and clopidogrel is as high as 50% in this situation.
   D. The risk of symptomatic hemorrhage in patients taking aspirin and clopidogrel is 8% in this situation.
   E. Patients who are taking aspirin and clopidogrel should receive a platelet transfusion and deamino-D-arginine vasopressin (DDAVP) before the procedure.

5. Regarding maintaining ventricular drain patency, are the following statements true or false?
   A. The clot can be flushed from the drain.
   B. The drain can be replaced.
   C. A second drain can be inserted.
   D. RtPA can be flushed into the drain if the patient can tolerate the drain being clamped for 1 hour. RtPA can be repeated every 12 hours as needed.

6. Regarding patients with external ventricular drains, are the following statements true or false?
   A. A post-drain insertion CT should be done to look for catheter-related hemorrhage.
   B. DVT prophylaxis can be undertaken with mechanical means before, during, and after the drain insertion.
   C. Unfractionated heparin VTE prophylaxis can be started 24 hours after the drain insertion.
   D. LMWH for VTE prophylaxis can be used before, during, and after the drain insertion.
   E. An inferior vena cava filter is an effective method to reduce the risk of DVT is patients who have a contraindication for chemical prophylaxis.

References


ANSWER KEY

1. A: False; B: False; C: False; D: True; E: True

2. A: True; B: False; C: True; D: True; E: False

3. A: False; B: False; C: True; D: True; E: False

4. A: False; B: False; C: True; D: True; E: True

5. A: True; B: True; C: True; D: True

6. A: True; B: True; C: True; D: False; E: False
Hematologic Adjuvant Treatment for Preventing and Treating Blood Loss in Pediatric Neurosurgery

Julia Sharma, John R.W. Kestle, and Ash Singhal

Pediatric blood loss can be a major concern during neurosurgical procedures, particularly during craniosynostosis, scoliosis, and tumor surgeries. When surgery is performed on young patients, such as craniosynostosis surgery, it is further complicated by lower preoperative hemoglobin levels and larger amounts of blood lost relative to total blood volume. This is due to hemoglobin levels reaching their physiological nadir (9–12 g/dL) at around 8 to 12 weeks of age. The infant head receives a proportionately greater percentage of blood volume, and this also contributes to a greater relative blood volume loss during cranial surgery. Moreover, fetal hemoglobin has a higher affinity for oxygen, such that less oxygen is off-loaded to tissues, which may accentuate the effects of blood loss in newborns and infants.

Blood loss can lead to major complications. According to the Pediatric Perioperative Cardiac Arrest (POCA) registry, 12% of intraoperative cardiac arrests in children are secondary to hypovolemia resulting from blood loss, with the majority of these events occurring during neurosurgical procedures. This clearly demonstrates that the pediatric neurosurgeon needs to consider blood loss very carefully, and plan strategies to minimize the risks posed to the child.

When compared with adults, children have higher rates of transfusion-related adverse events. In children, the most common adverse event seen in data collected through the Serious Hazards of Transfusion (SHOT) scheme in the United Kingdom was transfusion of an incorrect blood component, accounting for 82.2% of all adverse events. Other adverse events reported included acute transfusion reactions, delayed transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated graft-versus-host disease, and transfusion-transmitted infections. Infants seem to be at particularly high risk and have rates of adverse reactions nearly triple that of adults. Although adults have an estimated incidence of transfusion-related adverse events of 13 per 100,000 red cells, the incidence of an adverse event is estimated to be 18 per 100,000 red cells issued for children under 18 years old, and this number climbs to 37 per 100,000 for infants under 12 months of age. Despite the fact that these overall complication rates are low, many physicians and certainly the general public remain concerned about transfusions, particularly in children. Strategies to minimize blood loss and minimize the need for allogeneic blood transfusions are therefore of paramount importance in pediatric neurosurgery. This importance is reflected in the wealth of research and literature dedicated to treating and preventing pediatric blood loss during neurosurgical procedures. This chapter examines hematologic adjuvant treatments currently in use, and summarizes the recent evidence.

Venous thromboembolic events (deep venous thrombosis or pulmonary embolism) can be considered rare in this pediatric neurosurgery patient population and are not reviewed in this chapter.
Preoperative Strategies

There is much that can be done preoperatively to reduce the need for an allogeneic blood transfusion during surgery. The optimization of hematocrit (Hct) preoperatively is important, as a low Hct is predictive of an increased requirement for allogeneic blood transfusion. Furthermore, higher preoperative Hct levels facilitate a preoperative autologous donation (PAD), a strategy that can reduce the risk of receiving an allogeneic blood transfusion, which is discussed below.

Iron Supplementation

Preoperative iron supplementation has been shown to decrease the proportion of patients requiring blood transfusions in adults. It can be administered either orally or intravenously. Although there is insufficient evidence to support its routine preoperative use, it is inexpensive and has been used successfully as an adjunct to erythropoietin therapy to increase Hct in pediatric patients undergoing surgery where major blood loss is anticipated.

Erythropoietin

Studies looking at erythropoietin therapy to increase preoperative Hct have shown promise. In a randomized controlled study by Krajewski et al, the use of preoperative erythropoietin or Procrit (a recombinant protein that augments erythropoietin populations), given as weekly subcutaneous injections starting 3 weeks before surgery, increased preoperative Hct by 56.2% in children undergoing craniosynostosis surgery. Furthermore, the use of this strategy, in conjunction with intraoperative blood salvage, resulted in significantly lower allogeneic transfusion rates (5% vs 100% of the control group), as well as lower mean volumes transfused per patient (0.05 pediatric units versus 1.74 pediatric units in the control group). Similar studies have been done in pediatric spine surgery. Erythropoietin is particularly useful in patients who are unable or unwilling to receive blood transfusions.

Preoperative Autologous Blood Donation

Preoperative autologous blood donation (PABD) is a strategy whereby patients donate autologous blood that can be transfused as needed intraoperatively, thus reducing the need for allogeneic blood. It is a reasonable option for pediatric procedures where the amount of blood loss is expected to be at least 20% of the total blood volume. In pediatric neurosurgery, PAD is mainly used in scoliosis surgery, as patients tend to be older and are better able to tolerate donation. PAD is generally restricted to children who weigh over 20 kg but has been used in children as young as 3 months and with weights as low as 5.8 kg. It has the advantage of reducing the exposure of children to multiple donors and alleviates the demand on blood bank resources. Intraoperatively, it has the advantage over cell salvage of being ready to use without having to wait for a sufficient amount of blood loss/collection. In a review of 17 studies of PAD in children, allogeneic transfusions were avoided in 63% to 95% of patients through the use of PAD. Autologous blood wastage rates varied widely from 15 to 64%. The optimal time to donate continues to be a matter of some debate. Longer intervals between donation and surgery
allow for compensatory erythropoiesis to increase red blood cell volume, but carry the risk of hemolysis, which increases with longer storage intervals.

There are two pitfalls to the use of PAD. Children may have needle phobia, or they may become symptomatic from blood lost during the collection process.

Directed Donation

Directed donation is a process that allows family members to donate blood, in preparation for the patient’s surgery, that is reserved specifically for the patient. Although this option may be appealing to parents based on the assumption that this strategy might decrease the risk of infectious complications, a survey done at the Hospital for Sick Children in Toronto found that directed donors had 10-fold higher rates of transmissible disease compared with volunteer donors. However, this study did find that directed donation reduced exposure to multiple donors in an estimated 28% of patients, which is an important consideration for children who are at high risk of antibody formation when they receive blood products from several different donors. Some authors have raised the concern that directed donation carries a greater risk of the rare but highly lethal complication of graft-versus-host disease due to fact that human leukocyte antigen (HLA) homozygosity is more likely to occur among first-degree family members. Added to these risks are the ethical considerations of the loss of anonymity between donor and recipient, and the possibility of coercion into donation, as some family members may feel emotionally pressured to donate. In light of this, directed donation is not practiced routinely at most institutions.

Intraoperative Strategies

Intraoperative Blood Salvage

Intraoperative cell salvage systems are a commonly used blood-conservation technique whereby blood lost intraoperatively is collected, filtered, and transfused back to the patient once a sufficient quantity is available. A recent survey of current practice paradigms estimated that it is used in 26% of all craniosynostosis surgeries. Pediatric-sized systems have been developed and consist of downsized collection bowls. In adults, a recent Cochrane meta-analysis on the use of intraoperative cell salvage showed an absolute risk reduction of receiving an allogeneic blood transfusion of 21%. In pediatric neurosurgery, cell salvage has been shown to be effective at reducing exposure to allogeneic blood transfusion in scoliosis and craniosynostosis surgery. The main concern with intraoperative cell salvage is the risk of biological contamination. Microbiological growth in blood samples recuperated via cell salvage has been reported to be 38.5 to 68.4%. Despite these seemingly high contamination rates, no postoperative cultures were positive for the same species of bacteria found in the recuperated samples, suggesting that the reported contamination may not be clinically relevant.

Hypervolemic Hemodilution

Hypervolemic hemodilution (HH) involves hemodiluting a patient through infusion of a colloid solution, usually hydroxyethyl starch. Because this technique involves dilution of the patient’s circulating blood volume, the blood lost intraoperatively
will have a lower hematocrit, and a smaller red blood cell mass will be lost. Moreover, hemodilution improves tissue perfusion as decreased blood viscosity leads to decreased peripheral resistance. There is evidence that it is effective at reducing the amount of allogeneic blood transfused during scoliosis surgery in children.\textsuperscript{25}

**Acute Normovolemic Hemodilution**

Acute normovolemic hemodilution (ANH) also relies on the principle of hemodilution as a blood conservation strategy. It differs from HH in that an equal volume of blood is removed and stored before crystalloid or colloid infusion to keep the total blood volume stable. Advocates of this technique have argued that it carries the advantage over intraoperative cell salvage of being able to rapidly transfuse blood without having to wait for a specific quantity of blood loss to be recuperated and filtered. Despite these theoretical advantages, there is insufficient evidence to support the routine use of this technique.\textsuperscript{26} In a pediatric-specific randomized controlled study on patients undergoing craniosynostosis repair, the use of ANH had no effect on the amount of allogeneic blood transfused, risk of exposure to allogeneic blood, or the hematocrit value at hospital discharge.\textsuperscript{27} Furthermore, HH is simpler to use than ANH, and mathematical models have suggested that HH confers similar benefit and may be safer than ANH, particularly when blood losses are less than 40\% of total blood volume.\textsuperscript{28}

**Deliberate Hypotension**

The deliberate induction of hypotension is a controversial technique where blood pressure is lowered intraoperatively to minimize blood loss. In pediatrics, mean arterial pressures (MAPs) of 50 to 65 mm Hg or a MAP reduction of 20\% have been used as targets.\textsuperscript{21} This technique carries the risk of ischemia, and is contraindicated in patients with hypovolemia, elevated intracranial pressure, or decreased end-organ blood flow. Although potentially useful in older children undergoing spine surgery, deliberate hypotension is of limited use in cranial pediatric neurosurgery where cerebral perfusion is of paramount importance and with vasoactive anesthesia agents that induce a baseline level of hypotension to begin with.

**Antifibrinolytics**

Fibrin is the most basic structural element of a blood clot. Antifibrinolytics reduce perioperative bleeding by inhibiting the degradation of fibrin. The most commonly used antifibrinolytic drugs are aprotinin, tranexamic acid, and aminocaproic acid.

Aprotinin is a nonselective serine protease inhibitor derived from bovine lung. It acts via direct inhibition of plasmin, trypsin, plasma-kallikrein, and tissue-kallikrein.\textsuperscript{29,30} Tranexamic acid and $\varepsilon$-aminocaproic acid are synthetic lysine analogues that competitively inhibit activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin.

Several clinical trials have shown that antifibrinolytics such as aprotinin, tranexamic acid, and aminocaproic acid are effective at reducing blood loss and transfusion requirements in children undergoing neurosurgery.\textsuperscript{21,32} A Cochrane review done in children undergoing scoliosis surgery found that the risk of being transfused was similar in patients receiving antifibrinolytic drugs or placebo, but anti-
fibrinolytic drugs decreased the amount of blood transfused and the amount of blood lost.30 There is evidence that aprotinin may be more effective than other antifibrinolytics at reducing intraoperative blood loss.33,34 However, it was withdrawn from the worldwide market in 2007 after the Canadian antifibrinolytic trial (Blood conservation using Antifibrinolytics in a Randomized Trial [BART]) found an increased 30-day mortality and risk of cardiovascular complications with aprotinin when compared with other antifibrinolytics.33

**Recombinant Factor VIIa**

Recombinant factor VIIa (rFVIIa) is a hemostatic agent that enhances localized thrombin generation on thrombin-activated platelets at the site of injury, thereby enhancing platelet adhesion and aggregation.35 It is currently licensed for use in hemophiliac patients with inhibitors, but is being used off-label in certain unique situations to control intraoperative bleeding or neonatal intracranial hemorrhage in nonhemophiliac patients.36,37 The evidence to support its use intraoperatively is weak and largely based on subjective assessments of its hemostatic ability. In a recent retrospective review of 388 pediatric patients treated with off-label rFVIIa, 82% had subjective decrease in bleeding after its administration.35 There are only a few case reports and one case series addressing its use in pediatric neurosurgery, but the results are promising.38–40 In one case series by Heisel et al,38 rFVIIa was administered intravenously to eight pediatric patients to control life-threatening bleeding that failed to respond to standard neurosurgical technique and blood product replacement. In all but one case, there was an excellent response to rFVIIa with control of bleeding and successful completion of the procedure. One concern with the use of rFVIIa is the risk of thromboembolic adverse events. However, in two reviews of pediatric cases in which rFVIIa was used, the incidence was fairly low at 0.8 to 5.4%.35,41

**Desmopressin Acetate (DDAVP)**

Desmopressin acetate (deamino-8-D-arginine vasopressin, DDAVP) is a vasopressin analogue that has been used to correct bleeding time and provide surgical hemostasis for patients with von Willebrand disease, acquired platelet disorders, and uremia.42 It has also been used in normal patients to reduce blood loss during certain surgical procedures including cardiac surgery and complex spine surgeries. In adult studies, prophylactic DDAVP has been shown to reduce blood loss and transfusion requirements.43 In pediatric neuromuscular scoliosis, a randomized controlled trial showed that the administration of DDAVP immediately following induction of anesthesia resulted in a 19% reduction in overall blood loss, although this difference failed to reach significance.42

**Transfusion Protocols**

Transfusion triggers vary in different centers and depend on the particular clinical situation. During periods of rapid blood loss, hemodynamic parameters may be used to guide transfusion. For example, low hemoglobin/hematocrit levels in the presence of hypotension, tachycardia, metabolic acidosis, decreased peripheral perfusion, or low urine output may warrant transfusion.
Absolute transfusion triggers have been used by some institutions. A common threshold for transfusion is a hemoglobin level of less than 7 to 8 g/dL or a hematocrit of less than 0.21 to 0.3. In our institution, we have accepted hemoglobin levels as low as 5 g/dL in hemodynamically stable children as part of our initiative to decrease the rates of blood transfusion. Abandoning strict transfusion thresholds in conjunction with technical adjustments has decreased our transfusion rate from 42% to 11% in patients undergoing sagittal craniosynostosis correction.

There is increasing evidence that the use of transfusion algorithms can reduce allogeneic blood transfusions. In a randomized trial of 637 critically ill children, a transfusion threshold of 7 g/dL for red blood cell transfusion decreased transfusion requirements by 44% without an increase in adverse events. Moreover, 54% of patients in the restrictive-strategy transfusion group received no transfusion compared with only 2% in the liberal-strategy group.

Many clinicians advocate abandoning liberal transfusion strategies, and only providing transfusion at low hemoglobin thresholds (e.g., hemoglobin 7 g/dL), coupled with clinical evidence of hemodynamic instability.

**Conclusion**

The prevention and treatment of intraoperative blood loss is an important aspect of pediatric neurosurgery, as even a small volume of blood may represent a significant proportion of the child’s total blood volume. Furthermore, children have a higher incidence of transfusion-related adverse events, so reducing exposure to allogeneic blood products should be a key part of their perioperative management. In elective cases, erythropoietin and iron supplementation can be useful to augment Hct preoperatively. Preoperative autologous donation can be considered in select cases. Hemodilution strategies can be effective in reducing the risk of receiving an allogeneic blood transfusion, as they minimize the red blood cell volume lost for a given blood volume. Intraoperative blood salvage is now widely used in pediatric surgery, and there is good evidence that it reduces allogeneic blood transfusion rates. When blood loss is difficult to control intraoperatively, several agents may be used to achieve hemostasis, including antifibrinolytics, recombinant factor VIIa, and desmopressin acetate. Finally, the use of transfusion triggers and protocols has been shown to reduce the frequency of blood transfusions in children and should be implemented whenever possible.

**KEY POINTS**

- Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) are rare in the pediatric neurosurgery patient population.
- Infants reach a physiological nadir with regard to hemoglobin levels between 8 and 12 weeks of age (9–12 g/dL), and this may affect tolerance to the amount of surgical blood loss.
- Compared with adults, children (and particularly infants) have higher rates of transfusion-related adverse events but still remain low at 18 to 37 per 100,000.
- Preoperative strategies to reduce the need for allogeneic blood transfusion may include iron supplementation, erythropoietin, and autologous donation in older patients.
- Directed donation is currently not practiced at most institutions.
Intraoperative strategies to reduce the need for allogeneic blood transfusion may include using a blood salvage system, hypervolemic hemodilution, and antifibrinolytics.

Transfusion protocols/algorithms are important in the preoperative, intraoperative, and postoperative periods to guide transfusion requirements. They can successfully reduce allogeneic blood transfusions without impacting patient outcome.

REVIEW QUESTIONS

1. True or false:
   A. 12% of intraoperative cardiac arrests in pediatric surgery are secondary to hypovolemia resulting from blood loss.
   B. The incidence of transfusion-related events in children is 18 per 100,000.
   C. The incidence of transfusion-related events in infants is 37 per 100,000.
   D. The incidence of transfusion-related events in adults is 13 per 100,000.

2. True or false:
   A. Patients who are pretreated with erythropoietin typically start 3 to 4 weeks before surgery.
   B. Preoperative iron supplementation is recommended for all elective pediatric neurosurgery procedures.
   C. Autologous blood donation is recommended where possible for children undergoing scoliosis surgery.
   D. Directed donation is routine for all children < 3 years of age undergoing elective pediatric neurosurgery procedures.

3. True or false:
   A. Intraoperative blood salvage can be used for all major pediatric neurosurgical procedures.
   B. Intraoperative blood salvage is effective in reducing allogeneic blood transfusion in scoliosis and craniosynostosis surgery.
   C. The risk of clinically significant biological contamination with intraoperative blood salvage is very low.
   D. Hypervolemic hemodilution involves preoperative removal of blood and replacement with a colloid solution.
   E. Hypervolemic hemodilution involves infusion of a colloid solution.

4. True or false:
   A. Acute normovolemic hemodilution involves preoperative removal of blood and replacement with a crystalloid or colloid solution.
   B. Acute normovolemic hemodilution involves infusion of a colloid or crystalloid solution.
   C. Evidence supports the use of hypervolemic hemodilution for patients at risk for allogeneic blood transfusion.
   D. Evidence supports the use of acute normovolemic hemodilution for patients at risk for allogeneic blood transfusion.
   E. Evidence supports the use of deliberate hypotension to reduce blood loss for patients at risk for allogeneic blood transfusion.
5. True or false:
   A. Antifibrinolytics reduce perioperative bleeding by increasing the degradation of fibrin.
   B. Tranexamic acid and e-aminocaproic acid inhibit activation of plasminogen to plasmin.
   C. Aprotinin directly inhibits fibrin.
   D. Evidence does not support the selective use of antifibrinolytics to reduce blood loss for patients at risk for allogeneic blood transfusion.
   E. Antifibrinolytics do not change the risk of blood transfusion but reduce the amount of blood transfused and amount lost.

6. Regarding the need to proceed with blood transfusion in the pediatric neurosurgical patient, are the following statements true or false?
   A. A blood transfusion should not be started until physiological parameters (e.g., hypotension, decreased urine output, decreased peripheral perfusion) have developed.
   B. A common accepted threshold for blood transfusion is hemoglobin 9 g/dL.
   C. A common accepted threshold for blood transfusion is hemoglobin < 7 g/dL.
   D. An accepted strategy to determine need for blood transfusion when the hemoglobin is < 7 g/dL requires that the patient demonstrate hemodynamic instability.
   E. Transfusion algorithms can safely reduce allogeneic blood transfusion rates.

References


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Pediatric Neurosurgery–Specific Patient/Case Examples
Mark G. Hamilton and John R.W. Kestle

Anticoagulation management is not typically an important aspect of pediatric neurosurgical care. However, pediatric patients face significant risk with regard to blood loss issues related to weight and resultant blood volume and to immaturity of the hematopoietic system. This chapter presents specific cases to highlight strategies used to reduce blood loss and minimize allogeneic blood transfusion. The format for each case is standardized to illustrate the common themes for these clinical situations. For each case, a short discussion explains the course of action and provides other reasonable management options for similar circumstances.

Case 1: Craniosynostosis (Low Risk of Large Volume of Bleeding But High Risk of Transfusion)

History

A 6-month-old boy was referred to the craniofacial clinic for assessment of craniosynostosis. The child was otherwise well with a normal physical examination except for head shape features consistent with sagittal synostosis. The referring physician had ordered a computed tomography (CT) scan of the head, which confirmed the diagnosis of sagittal synostosis (Fig. 29.1). It is not usual practice to do CTs when the clinical diagnosis is straightforward. However, the figures illustrate the head shape features and the fused sagittal suture. Surgery was offered to correct the calvarial deformity.

Procedure

Preoperatively, the child weighed 8.3 kg and had a preoperative hemoglobin of 12.2 g/dL with an estimated blood volume of 660 mL. Platelet count, international normalized ratio (INR), and partial thromboplastin time (PTT) were all normal. Directed donor blood was not done for the procedure. The intraoperative plan for potential transfusion was reviewed with the anesthesiologist. Two intravenous (IV) lines (one a central line) and an arterial line were inserted. Hypervolemic hemodilution was initiated with crystalloid solution. The threshold for transfusion was set for at a hemoglobin of 6 to 7 g/dL depending also on physiological parameters (blood pressure, heart rate, central venous pressure [CVP], and urine output). A 10% blood volume loss would result from 65 mL of blood loss. The operating room was kept warm until the child was fully covered and a warming blanket was functioning. Normothermia was carefully maintained throughout the procedure. Mea-
The surgical procedure involved a bicoronal incision with a bifrontoparietal craniotomy followed by multiple barrel stave temporal bone cuts, remodeling of the bone before reattachment, and resultant cranial anteroposterior (AP) shortening using resorbing plates. Meticulous attention was paid to bleeding during the procedure. The scalp incision was done with scoring of the skin followed by use of monopolar (with a needle tip) and bipolar cautery to divide the subcutaneous tissue and control scalp bleeding. Bone bleeding was controlled with bone wax, frequently using the monopolar cautery to score the bone to help the bone wax adhere. One small bur hole was used for access, and the bifrontoparietal craniotomy was performed. Bone edge bleeding was controlled with bone wax. Dural oozing was dealt with using Surgicel, surgical patties, and Gelfoam, and warm, wet lap sponges. Scalp closure was accomplished with resorbing galeal and skin sutures.

Intraoperative assessments of the child’s hemoglobin were 9.2 and 8.9 (above threshold for transfusion). Postoperative hemoglobin was 7.0 on day 3, but the child was well, with normal physiological parameters. Transfusion was not required. Postoperative iron supplementation (for 2 month duration) was started at the time of discharge from hospital.

**Discussion**

The patient underwent a surgical procedure that has low potential for significant blood loss but high probability of requiring a blood transfusion. It is the responsibility of the pediatric neurosurgeon to discuss with the anesthesiologist the potential for blood loss and the measures that are required to minimize blood loss so as to minimize the need for allogeneic blood transfusion and to establish a transfusion threshold to avoid unnecessary blood transfusion. Hypervolemic hemodilution was undertaken prior to starting the procedure. This does not affect coagulation but may reduce the total amount of red blood cell loss.

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**Fig. 29.1a,b** (a) A three-dimensional (3D) computed tomography (CT) scan of the head showing the left side of the skull with patent coronal, lambdoid, and squamosal sutures. Frontal bossing is present. (b) A 3D CT scan of the head showing view of left posterior lateral aspect of skull with patent coronal, lambdoid, and squamosal sutures. Synostosis of the sagittal suture is evident by the ridging (arrows).
It is important to establish a temperature-controlled operating room environment and to ensure that hypothermia does not occur. Adequate venous access for infusion of crystalloid/colloid or blood is essential. Blood loss must be measured and physiological parameters monitored. Meticulous attention must be paid to maintaining hemostasis. It is important to alert the anesthesiologist to any excessive or unexpected bleeding. The time of highest potential risk for catastrophic hemorrhage (although a very low overall risk) is during the performance of the craniotomy in relation to the large venous sinuses (e.g., sagittal sinus).

It is equally important to discuss transfusion thresholds with the pediatric intensive care unit (ICU) physicians to avoid unnecessary blood transfusions. This child was also given iron supplementation after discharge to facilitate replenishment of iron stores.

Strategies that were not undertaken in this case include the use of antifibrinolytics or a cell saver. Although an argument could be made for the use of an antifibrinolytic, it is not routine practice for this type of surgery at our institution. Cell savers are problematic in children of this size where the significance of the amount of blood loss is directly related to the small total blood volume that is at risk and because there is a small potential for catastrophic hemorrhage; typically more blood is collected in patties and sponges than with suction.

In addition, in a younger child, it may have been feasible to do an endoscopic cranial vault remodeling, which entails a shorter duration of surgery and potentially less blood loss.

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**Case 2: Brain Tumor with High Vascularity (High Risk of Large Volume of Bleeding and High Risk of Transfusion)**

**History**

A 5-year-old girl presented with an exacerbation of a slowly progressive 3-month history of headache with morning vomiting and lethargy. She had no other relevant past medical history. She was sleepy but would awaken with stimulation. She had a right cranial nerve VI partial palsy and bilateral papilledema. There was no focal motor weakness. She was ataxic but able to walk independently. A head CT scan demonstrated significant hydrocephalus with a large hyperdense lesion/tumor in the left posterior lateral ventricle with evidence of a large feeding vessel (Fig. 29.2a). A magnetic resonance imaging (MRI) scan provided additional information regarding the lesion. The tumor was densely enhancing and was associated with multiple feeding vessels, with the largest located anterior to the tumor representing choroid vessels and evidence of large vessels within the tumor (Fig. 29.2b,c). The presumptive diagnosis was that this most likely represented a choroid plexus carcinoma or less likely a choroid plexus papilloma. MRI of the spine did not identify and evidence of tumor. Urgent surgery was recommended. Decadron was administered. A consultation was undertaken with a neuroradiologist to determine if any opportunity existed for preoperative embolization, but this was not felt to be a feasible option in this patient.

**Procedure**

Preoperatively, the child weighed 18.5 kg and had a preoperative hemoglobin of 14.2 g/dL with an estimated blood volume of 1,500 mL. Platelet count, INR, and PTT
were all normal. The intraoperative plan for potential transfusion was reviewed with the anesthesiologist. Two IVs (one a central line) and an arterial line were inserted. Hypervolemic hemodilution was initiated with crystalloid solution and colloid solution. Tranexamic acid was administered preoperatively. The threshold for intraoperative transfusion was set at a hemoglobin of 7 g/dL depending also on

Fig. 29.2a–d  (a) Axial unenhanced CT scan of the head demonstrating hydrocephalus and a large hyperdense posterior left lateral ventricular mass with a large vessel anterior to the mass (arrow). (b) Axial T1-enhanced magnetic resonance imaging (MRI) scan of the head demonstrating hydrocephalus and a large hyperdense posterior left lateral enhancing ventricular mass with a large vessel anterior to the mass (arrow) and vessels traversing the tumor. (c) Sagittal T1-enhanced MRI scan of the head demonstrating hydrocephalus and a large hyperdense posterior left lateral enhancing ventricular mass with large vessels anterior to the mass. (d) Axial HASTE (Half-Fourier Acquisition Single Shot Turbo Spin Echo) MRI scan of the head done 5 years after diagnosis demonstrating stable ventriculomegaly, evidence of artifact from the right parietal shunt, and no evidence of tumor in the left lateral ventricle. Additional full MRI sequences with and without enhancement (spine and brain) demonstrated no evidence of any tumor recurrence.
the rate of blood loss and physiological parameters (blood pressure, heart rate, CVP, and urine output). A 10% blood volume loss would result from 150 mL of blood loss. The operating room was kept warm until the child was fully covered and a warming blanket was functioning. Normothermia was carefully maintained throughout the procedure. Measurement of blood loss was accomplished with monitoring of suction and weighing of all surgical sponges.

The surgical procedure involved a left parietal craniotomy with a transcortical approach to the tumor. Image guidance was used to outline the tumor and assist with planning a trajectory along the front of the tumor to allow access to the main feeding vessels, which were clipped and coagulated. However, even with obliteration of the anterior feeding vessels the tumor remained very vascular until the end of the resection. Total blood loss was 500 mL (35% blood volume). The patient received a transfusion of allogeneic blood (250 cc packed red blood cells) when estimated blood loss was 150 mL. Physiological parameters remained stable throughout the surgical procedure. Clotting parameters (platelets, INR, PTT) remained normal throughout the procedure. Minor bleeding was dealt with using Surgicel, surgical patties, and Gelfoam. A gross total resection of the tumor was accomplished. An external ventricular drain (EVD) was inserted at the end of the procedure. Scalp closure was accomplished with resorbing galeal and skin sutures.

The final pathological diagnosis was choroid plexus carcinoma. The patient was weaned off the EVD, but a ventriculoperitoneal shunt was eventually required. Adjuvant therapy for the tumor diagnosis was provided and the patient remains tumor free 5 years postdiagnosis (Fig. 29.2d), with no motor, sensory, language, or significant cognitive difficulties.

**Discussion**

This child underwent a surgical procedure that had a high probability for significant blood loss and a high probability for requiring a blood transfusion. It is the responsibility of the pediatric neurosurgeon to discuss with the anesthesiologist the potential for blood loss and the measures that are required to minimize blood loss so as to minimize the need for allogeneic blood transfusion and to establish a transfusion threshold to avoid unnecessary blood transfusion. Hypervolemic hemodilution was undertaken with both crystalloid and colloid solutions prior to starting the procedure. This does not affect coagulation but may reduce the total amount of red blood cell loss. The threshold for transfusion was determined, but was set with a proviso that the rate of blood loss (i.e., if there was a significant rate of hemorrhage at any time) could override the need to have a hemoglobin fall to the threshold level. Platelet levels and coagulation parameters were carefully followed during the surgery and remained stable. Factor concentrate, fresh frozen plasma (FFP), and platelets were available if needed but not required. An intraoperative transfusion was required, with the total estimated blood loss representing one third of the patient’s total blood volume. The first postoperative hemoglobin was 80 g/dL. Tranexamic acid was administered preoperatively but probably did not make a significant contribution to controlling bleeding.

It is important to establish a temperature controlled operating room environment and to ensure that hypothermia does not occur. Adequate venous access for infusion of crystalloid/colloid or blood is essential. Blood loss must be measured and physiological parameters monitored. Meticulous attention must be paid to maintaining hemostasis. It is important to alert the anesthesiologist to any excessive or
unexpected bleeding. In this case, blood loss was relatively constant throughout the actual tumor resection.

It is equally important to discuss transfusion thresholds with the pediatric ICU doctors to avoid unnecessary blood transfusions.

A strategy that was not undertaken in this case is the use of a cell saver. Cell savers cannot be used in the setting of tumor resection. In addition, the issue of preoperative tumor embolization was explored but not deemed feasible for this patient. One could make an argument for proceeding with a cerebral angiogram with the option of embolization if the vascular anatomy is compatible with directing a catheter into the primary tumor vessels.

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**Case 3: Arteriovenous Malformation with Intracerebral Hemorrhage (High Risk of Large Volume of Bleeding and Indeterminate Risk of Transfusion)**

**History**

A 12-year-old boy presented with a severe sudden-onset headache followed shortly thereafter by a seizure and a protracted postictal period. The first neurosurgical clinical examination demonstrated a Glasgow Coma Scale (GCS) score of 13, pupils equal and reactive, and no obvious lateralizing signs. A CT scan showed a large right frontal intraparenchymal hemorrhage with intraventricular extension (Fig. 29.3a). CT angiography demonstrated abnormal vessels consistent with a Spetzler-Martin grade 2 arteriovenous malformation (AVM) (Fig. 29.3b). Preoperative angiography was done urgently under general anesthesia to evaluate the vascular anatomy and determine if preoperative embolization was possible. The angiogram confirmed the vascular anatomy, did not identify any intranidal aneurysm, and was not felt to be compatible with an attempt for embolization (Fig. 29.3c). The patient’s was then brought emergently to the operating room.

**Procedure**

Preoperatively, the child weighed 51 kg and had a preoperative hemoglobin of 15.2 g/dL with an estimated blood volume of 4,000 mL. Platelet count, INR, and PTT were all normal. The intraoperative plan for potential transfusion was reviewed with the anesthesiologist. Two IVs (one a central line) and an arterial line were inserted. Hypervolemic hemodilution was initiated with crystalloid solution. Blood pressure control was discussed with the anesthesiologist with the aim to maintain the mean pressure ± 10 mm Hg. The threshold for intraoperative transfusion was set at a hemoglobin of 8 g/dL depending also on the rate of blood loss and physiological parameters (blood pressure, heart rate, CVP, and urine output). A 10% blood volume loss would result from 400 mL of blood loss. The operating room was kept warm until the patient was fully covered and a warming blanket was functioning. Normothermia was carefully maintained throughout the procedure. Measurement of blood loss was accomplished with monitoring of suction and weighing of all surgical sponges.

The surgical procedure involved a right frontal craniotomy with a transcortical approach to the clot to decompress the mass effect and then a direct approach to the AVM arterial feeding vessels. The AVM was resected and the entire clot was
removed. The entry into the right frontal ventricular horn was identified, and blood was aspirated from the ventricle before placing and external ventricular drain (EVD). Total blood loss was 300 mL (9% of blood volume). The patient did not require or receive a transfusion of allogeneic blood. Physiological parameters remained stable throughout the surgical procedure. Clotting parameters (platelets, INR, PTT) remained normal throughout the procedure. Minor bleeding was dealt with using Surgicel, surgical patties, and Gelfoam. Scalp closure was accomplished with resorbing galeal sutures and skin staples.

The boy did well postoperatively. Postoperative angiography confirmed total resection of the AVM. The EVD was weaned and a shunt was not required. He continues to do well 2 years after resection of his AVM with no obvious motor, sensory, or significant cognitive difficulties.

**Discussion**

This child underwent a surgical procedure that had a high probability for significant blood loss and an indeterminate probability for requiring a blood transfusion.
It is the responsibility of the pediatric neurosurgeon to discuss with the anesthesiologist the potential for blood loss and the measures that are required to minimize blood loss so as to minimize the need for allogeneic blood transfusion and to establish a transfusion threshold to avoid unnecessary blood transfusion. Hypervolemic hemodilution was undertaken with crystalloid solution prior to starting the procedure. This does not affect coagulation but may reduce the total amount of red blood cell loss. The threshold for transfusion was determined but was set with a proviso that the rate of blood loss (i.e., if there was a significant rate of hemorrhage at any time) could override the need to have a hemoglobin fall to the threshold level. Platelet levels and coagulation parameters were carefully followed during the surgery and remained stable. Factor concentrate, FFP, and platelets were available if needed but not required. Blood loss was 400 mL, which represented < 10% of total blood volume, and his physiological parameters remained stable throughout the surgery.

It is important to establish a temperature-controlled operating room environment and to ensure that hypothermia does not occur. Adequate venous access for infusion of crystalloid/colloid or blood is essential. Blood loss must be measured and physiological parameters monitored. Meticulous attention must be paid to maintaining hemostasis. It is important to alert the anesthesiologist to any excessive or unexpected bleeding. In this case, blood loss was relatively constant throughout the AVM resection and clot removal.

It is equally important to discuss transfusion thresholds with the pediatric ICU physicians to avoid unnecessary blood transfusions.

Strategies that were not undertaken in this case include the use of antifibrinolytics or a cell saver. Although an argument could be made for the use of an antifibrinolytic, it is not routine practice for this type of surgery at our institution. It can be reasoned that although the use of a cell saver may not eliminate the possibility of an allogeneic transfusion, it might reduce the volume of allogeneic blood that is required. However, the actual value in this type of surgical scenario (emergency AVM resection) has not been evaluated. In addition, this patient also started with a normal hemoglobin and a 4,000-mL estimated blood volume.

### Case 4: Chiari 1 Malformation with Hydrocephalus and Syringomyelia (Low Risk of Large Volume of Bleeding and Low Risk of Transfusion)

#### History

A 16-year-old boy presented with a 2-year history of headache and deterioration in school performance. His headaches were initially intermittent and associated with straining, bending over, cough, and physical activity. The headaches had become more constant but with the same pattern of exacerbation and was affecting his ability to participate in school and afterschool activities. In addition, his school performance had deteriorated significantly. His neurologic examination was normal, with the exception of a minor problem with tandem gait. He did not have papilledema. His pediatrician had ordered an MRI scan, which identified a Chiari 1 malformation with associated hydrocephalus and syringomyelia (Fig. 29.4). Surgery was recommended. A posterior fossa craniectomy and duraplasty to decompress the Chiari 1 malformation was the initial recommended procedure.
Procedure

Preoperatively, the child weighed 65 kg and had a preoperative hemoglobin of 15.8 g/dL with an estimated blood volume of 5,200 mL. Platelet count, INR, and PTT were all normal. The intraoperative plan for potential transfusion was reviewed with the anesthesiologist. Two IVs and an arterial line were inserted. The threshold for intraoperative transfusion was set at a hemoglobin of 7 g/dL depending also on the rate of blood loss and physiological parameters (blood pressure, heart rate, CVP, and urine output). A 10% blood volume loss would result from 500 mL of blood loss. The operating room was kept warm until the patient was fully covered and a warming blanket was functioning. Normothermia was carefully maintained throughout the procedure. Measurement of blood loss was accomplished with monitoring of suction and weighing of all surgical sponges.

The surgical procedure involved a posterior fossa craniectomy and C1 laminectomy with duraplasty using a synthetic graft. A midline muscle-sparing opening was accomplished. There was minimal bleeding during this part of the procedure. The muscle was stripped off the suboccipital bone and the arch of C1, sparing the muscle caudal to the top of C2. The bone removal was accomplished with a combination of high-speed drill and rongeurs. Bone bleeding was dealt with in an ongoing basis using bone wax. The epidural veins were kept intact. Any bleeding from the epidural space was managed using Surgicel, Gelfoam, and surgical patties. The dural opening was a classic Y shape. However, the dural opening was started at the C1 level and advanced rostrally to cross the level of the foramen magnum, and 1 cm above this level was split to diverge toward each of the two rostral craniectomy corners. The initial dural opening was accomplished using sharp dissection. A curved instrument similar to a Penfield Number 3 dissector but approximately one-third diameter was slipped under the dura, elevating the dura, and advanced rostrally as the dura was cauterized with a needle tip cautery at very low settings. This offers the advantage of instant coagulation of most dural bleeding. The poten-
tial risk points for opening the posterior fossa dura are at the level of the foramen magnum where a patent ring venous sinus may exist, or immediately superior to this level where a midline sinus connecting the foramen magnum level ring sinus may be present and connect to the torcular. The caudal-to-rostral approach provides excellent control of any potential anatomic variations in venous or venous sinus anatomy. To be prepared, hemostasis clips and bipolar cautery are essential. Dural retraction sutures were placed at approximately 2- to 3-cm intervals. The arachnoid was left intact, and a dural patch was cut and sutured into the dural opening. A Gelfoam layer was placed over the dura, and a standard multilayer closure with resorbing suture was then used for the wound closure.

Total blood loss was less than 50 mL (< 1% blood volume). The patient did not require or receive a transfusion of allogeneic blood. Physiological parameters remained stable throughout the surgical procedure. Clotting parameters (platelets, INR, PT) were not reassessed during the procedure.

The boy did well postoperatively. At his 4-week postoperative assessment his headaches were noted to have resolved. His 3-month postoperative MRI confirmed both decompression of the Chiari 1, a significant reduction in his ventriculomegaly (hydrocephalus), and resolution of the syrinx. No other treatment of his hydrocephalus was required. He continues to do well 2 years later, with no headaches and no obvious motor, sensory, or significant cognitive difficulties.

Discussion

This child underwent a surgical procedure that had a low probability for significant blood loss and a low probability for requiring a blood transfusion. It is the responsibility of the pediatric neurosurgeon to discuss with the anesthesiologist the potential for blood loss and the measures that are required to minimize blood loss so as to minimize the need for allogeneic blood transfusion and to establish a transfusion threshold to avoid unnecessary blood transfusion. The threshold for transfusion was determined but was set with the understanding that the expected amount of blood loss was small.

It is equally important to discuss transfusion thresholds with the pediatric ICU doctors to avoid unnecessary blood transfusions. In this case it is unlikely that there would be any significant chance that a postoperative transfusion would be considered.

Strategies that were not undertaken in this case include the use of antifibrinolytics or a cell saver. The risk of significant blood loss is so low that neither would be considered reasonable in this situation.

References

Index

Note: Page references followed by $f$ or $t$ indicate figures or tables, respectively.

A

Abciximab
action mechanism of, 200$t$
antiplatelet activity of, 203
clinical applications of
arterial dissection, 324
endovascular procedures, 313
intracranial stenting, 310, 321–322
ischemic stroke, 300–301
half-life of, 203
reversal of, 200$t$
ABO blood type, 87, 88, 99
Acenocoumarol, 200$t$, 201
Acetylsalicylic acid (ASA).
See also Aspirin
clinical applications of
arterial dissection, 325–326
intracranial aneurysm, 320
stroke, 273
Adenosine diphosphatase, 20
Adenosine diphosphate, 74
Adenosine diphosphate receptor
inhibitors, 208. See also Clopidogrel; Prasugrel; Ticlopidine
Adenosine diphosphate test
of bleeding time, 87
of resistance to anticoagulants, 313
Albumin, 90
Alcohol abuse, 347–348, 348$f$
American College of Chest Physicians
guidelines, 208
for anticoagulation, 282
for antiplatelet agents, 168
for antithrombotic therapy, 7, 7$t$–8$t$
for heparin, 172
for perioperative thromboembolism
risk stratification, 209, 211, 211$t$
for postoperative resumption of anticoagulant and antiplatelet therapy, 209
for venous thromboembolism prevention and treatment, 117–118, 136
for vitamin K antagonist manage-
ment, 48, 49$t$
American Heart Association guide-
lines, for intracerebral hemorrhage management, 280, 281, 282
Aminocaproic acid, 77, 270, 387
Amyloid angiopathy, 277, 283
Anemia, 85, 92
Aneurysm clips, 73
Aneurysms, intracranial
anteroar communicating artery, 322–324, 323$f$
coil embolization of, 312–313, 320–324, 321$f$, 323$f$
case example of, 320–322, 321$f$
intraprocedural rupture of, 322–324, 323$f$
microcoils for, 224–225
of subarachnoid aneurysm, 378
thrombus formation during, 312–313, 320–322, 321$f$
hypophyseal, 320–322, 321$f$
rupture of, 272–273, 273$t$, 309
anticoagulant drug-related, 273–274
during coil embolization, 322–324, 323$f$
stenting of, 309, 315, 320–322, 321$f$, 378, 379
unruptured, 272–275
anticoagulation therapy in, 274–275
antiplatelet agent therapy in, 273–274
Angiography
- of aneurysms, 320, 321f, 322–323, 323f
- anticoagulant use prior to and during, 307–309
digital subtraction, 189
- 3-dimensional road map technique of, 221–222, 232
- in embolization procedures, 220, 221–222, 225
- of internal artery dissection, 324, 325, 325f
- of intraparenchymal hemorrhage, 318, 319f
- pulmonary, 125
Anisindione, 200t, 201
Anticoagulants. See also specific anticoagulants
- as bridging therapy, 211–212
- as coagulation-type bleeding disorder cause, 43
discontinuation prior to surgery, 376, 380
effect on thrombotic disorders test results, 38, 39t
indications for, 47, 331
- as intracranial hemorrhage cause, 332
for neuroendovascular procedures
- patient/case examples of, 318–330
- reversal of, 313–314
new, 130–135
for nonsurgical, non-venous thromboembolism conditions, 167–183
postoperative resumption of, 209, 211–216, 314–315, 376
- reversal of, 75, 76t, 199–202, 200t, 301, 313–314, 378, 380
- in traumatic brain injury
management guidelines for, 334–335, 334f, 335f
resumption after injury, 336–338
Antifibrinolytics, use in pediatric patients, 387–388, 397, 402, 404
Antiphospholipid syndrome, 41
Antiplalet agents, 55-56. See also specific antiplatelet agents
as aneurysm rupture risk factor, 273–274
- in cardiovascular disease, 167–170
in cardiac stenting, 168–169, 170f, 171f, 178–179
classes of, 208
discontinuation prior to surgery, 265, 370–371, 376, 380
indications for, 332
- as intracerebral hemorrhage risk factor, 282–283
postoperative resumption of, 209, 211–216, 314–315, 376
- reversal of, 56, 57t, 75, 76t, 200t, 202–204, 313–314, 378, 380
- for stenting, 309–310
in subarachnoid hemorrhage, 313
in traumatic brain injury
management guidelines for, 334–335, 334f, 335f
preinjury use of, 332, 333, 333f, 334f
resumption after injury, 336, 337–338
Antithrombin coagulation pathway, 20
Antithrombin deficiency, 39t
Antithrombotic agents, new, 173, 175
Apheresis, 100
Apixaban, 130–131, 131t
- discontinuation prior to surgery, 176
half-life of, 176
- interruption of treatment with, 133
resumption after surgery, 176
reversal of, 133
- as venous thromboembolism treatment, 133–135
Aprotinin, 77, 371, 387, 388
Argatroban, 54–55, 200t, 201, 309
Arteriovenous malformation clips, 73
Arteriovenous malformations
- anticoagulant and antiplatelet drug use in, 276, 284
- in endovascular treatment, 314, 318–319, 319f
as intracerebral hemorrhage cause, 275–276, 276f
in pediatric patients, 400–402, 401f
preoperative embolization of, 222–223, 225, 229–230
Ascending pharyngeal artery, preoperative embolization of, 226, 228
Aspirin
action mechanism of, 200t, 210t
as aneurysm rupture cause, 284
anticoagulant/antiplatelet activity of, 55–56, 202–203, 210t, 332
clinical applications of
myocardial infarction prophylaxis, 167
neuroendovascular procedures, 313
stenting procedures, 309–310
cyclooxygenase-1-inhibiting activity of, 332
discontinuation prior to surgery, 168, 210t, 376
half-life of, 202, 210t
as perioperative bleeding cause, 264–265
postoperative resumption of, 208, 315
reversal of, 56, 57, 76f, 200t
therapeutic dosage of, 210t
Atrial fibrillation
anticoagulant therapy in, 170–173, 171f
as stroke risk factor, 170–172, 171f, 171t, 179, 279–280, 279t, 292, 308
warfarin therapy for, as chronic subdural hematoma cause, 349–351
Avitene, 242t–243t, 246

B
Bacterial contamination, of transfused blood, 88–89
Bacterial infections, cerebral venous sinus thrombosis-related, 186t, 190
Bebulin, 106
Bernard-Soulier disorder, 42–43
Bevacizumab, concurrent use with anticoagulants, 262
Bivalirudin, 54, 200t, 201
Bleeding disorders
cogulation-type, 31, 31t
acquired, 43
inherited, 43
symptoms of, 42
differentiation of, 31, 31t
hemostasis screening test results in, 32, 33t
platelet-type, 31, 31t
Bleeding history, 85
Bleeding risk, preoperative assessment of, 85
Bleeding time (BT) measurement of, 29, 87 prolonged, 284
Blood, constituents of, 72
Blood-borne pathogen screening, of donated blood, 99
Blood conservation strategies, for Jehovah’s Witnesses, 94–95, 103–104
Blood donations autologous, 102–103
in pediatric patients, 385–386
collection, processing, and storage of, 99
directed, 102, 103, 386
Blood factor replacement, 90–95
Blood group antigen incompatibility, 100
Blood loss, intraoperative factors affecting, 72–73
monitoring of, 89
physiological impact of, 73–74, 81
prevention/minimization of. See also Hemostasis
with embolization, 219–236
with surgical techniques, 77, 80, 81
principles of, 71–84
Blood product replacement. See Blood replacement
Blood products, adverse reactions to, 88–89, 106–109
delayed hemolytic, 100, 108–109
febrile nonhemolytic, 99–100, 107
Blood products, adverse reactions to (continued)
   hemolytic, 88, 100, 107, 108–109
   in pediatric patients, 384, 389
   transfusion-related acute lung injury (TRALI), 108, 384
Blood replacement, 85–113
   autologous and directed blood donations, 85, 102–103, 385–386
   blood factors, 90–95
   blood product transfusions, 90–95
   in cranial surgery, 92
   in Jehovah’s Witnesses, 94–95, 103–104
   leukodepletion and irradiation in, 99–100
   plasma components, 104–106
   platelet donations, 100
   platelet transfusions, 102
   preoperative assessment for, 85–88
   red blood cell transfusions, 100–102
   in spinal surgery, 93
Blood salvage
   autologous, 93, 96
   in pediatric patients, 386
Blood salvage devices, 371
   cell savers, 93, 96, 104, 371, 397, 402, 404
Blood smears, peripheral, 28
Blood substitutes, 104
Blood transfusions
   adverse reactions to. See Blood products, adverse reactions to
   autologous, 85
   massive, 89, 92
   in pediatric patients, 388–389, 397, 400
   religious belief-based refusal of, 94–95, 103–104
Blood typing and crossmatching, 87–88
Blood vessels, antithrombotic activities within, 21f
Blood volume
   average, 72
   as percentage of total body weight, 72, 81
Blunt trauma, as stroke cause, 299–300, 303
Bone tumors, spinal, preoperative embolization of, 231
Bone wax, 77, 78t, 242t–243t, 247–248, 251
Bovie, William T., 241, 249
Brain injury. See also Traumatic brain injury
   as coagulopathy cause, 72–73
   platelet dysfunction in, 92
Brain natriuretic peptide (BNP), 123, 125
Brain tumor patients
   antiplatelet therapy in, 264–265
   venous thromboembolism in, 119–120, 259
   prophylaxis against, 260–262
   treatment of, 136, 137, 263–264
Brain tumors
   anticoagulant-associated intracranial hemorrhage within, 259–260
   with high vascularity, in pediatric patients, 397–400, 398f
n-Butyl cyanoacrylate (NBCA), 223–224, 225, 226, 227, 228, 229
C
Cancer. See also specific types of cancer
   venous thromboembolism associated with, 40, 136
Cardiac arrest, in pediatric patients, 384
Cardioembolization, 292
Cardiovascular disease
   antiplatelet agent use in, 167–170
   bridging anticoagulant therapy for, 208–209
   stent use in. See Stents/stenting, cardiac
   warfarin anticoagulation in, 208
Carotid artery, stenting of, 324–326, 325f
Carotid endarterectomy, as ischemic stroke treatment, 299
Catheters
   brain, 375–379, 380–381
   for embolization, 219, 220, 221
spinal, 379–381
thrombus formation on, 308, 312
Caustics, as hemostatic agents, 241–242
Cautery
bipolar, 249–250, 251
monopolar (unipolar), 241, 249, 251
Cavernous malformations, 276–277, 284
Cell salvage, intraoperative, 92, 96.
See also Cell savers
Cell savers, 93, 96, 104, 371
use in pediatric patients, 397, 402, 404
Cellulose, oxidized, 78t, 242t–243t, 244–246, 251
regenerated, 242t–243t, 244–246
Cerebral venous sinus thrombosis, 184–196
case examples of, 191, 192f–193f
definition of, 184
diagnosis of, 186–188, 193
epidemiology of, 184–185
etiology of, 185
neuroimaging of, 188–189, 188f
pathology of, 185, 186f
prognosis of, 189–190
sagittal, 344–345, 345f
treatment of, 190–191, 328–330, 329f
Cerebrospinal fluid leaks, 248, 380
Cerebrospinal fluid shunts, 375–377
Cerebrovascular disease. See also Stroke
Clots, for bleeding control, 73
Clopidogrel, 56
action mechanism of, 76, 200t, 210t
adverse effects of, 370–371
anticoagulant activity of, 210t
antiplatelet activity of, 203, 332
clinical applications of
arterial dissection, 325–326
endovascular procedures, 313
ischemic stroke, 300
stenting, 309–310
comparison with prasugrel, 176
discontinuation prior to surgery, 168–169, 210t, 215, 370–371, 376
half-life of, 210t
resistance to, 309, 313
resumption after surgery, 208, 315, 371
reversal of, 56, 57, 76t, 200t, 203
therapeutic dosage of, 210t
Coagulation
acquired defects in, 269
pathways in, 19–20, 19f
substrates of, 72
Coagulation cascade, 17, 74–75, 269–272, 270f, 271f, 272f
regulatory mechanisms of, 20, 21f
Coagulation factors. See also specific coagulation factors
activation of, 19, 19f, 271f
half-lives of, 105, 106
measurement of levels of, 22, 22f
preoperative measurement of, 27, 28
in vitamin K antagonist reversal, 48–49
Coagulation status, perioperative, 72
Coagulation testing, 204
postoperative, 209
preoperative, 26–37
abnormal values in, 32, 33t, 34f
assessment strategies for, 30–32, 32f, 35
common tests in, 27–28
limitations of, 29–30
randomized clinical trials of, 26–27
uncommon tests in, 28–29
Coagulopathies
heparin-related, treatment of, 52–53
Coagulopathies (continued) as intracerebral hemorrhage cause, 277

Collagen, microcrystalline/microfibrillar, 79t, 242t–243t, 246

Collagen test, of bleeding time, 87

Colloid solutions, 72, 90, 95, 397, 399, 402

Compression devices pneumatic, 381 intermittent, 282, 367, 368, 370 sequential, 153, 260

Computed tomography angiography, for pulmonary embolism diagnosis, 123f, 124

Coronary artery disease, 264

Coumadin, 76, 376

Coumarins, 201–202. See also Warfarin

Cranial nerve palsy, embolization-related, 228–229

Cranial sinus venous thrombosis. See Cerebral venous sinus thrombosis

Cranial surgery, coagulation and bleeding management in blood replacement in, 92 patient/case examples of, 343–352

Cranial venous sinus thrombosis. See Cerebral venous sinus thrombosis

Craniectomy, decompressive suboccipital, 297–298, 303

Craniostenosis, 395–397, 396f

Craniotomy antiplatelet therapy-related hemorrhage with, 264 blood loss management in, 80 deep vein thrombosis prophylaxis for, 154f, 155–156 as venous thromboembolism risk factor, 119–120

Crystalloid solutions, 90, 95 use in pediatric patients, 397, 399, 402

Cushing, Harvey, 71, 249

Cyanoacrylates, as embolic agents, 223

Cyclooxygenase inhibitors. See Aspirin

Cytomegalovirus, transmission in blood transfusions, 88, 100

D

Dabigatran, 55, 131–132, 131t action mechanism of, 175, 200t adverse effects/disadvantages of, 75, 132, 175, 343–344, 344f clinical pharmacology of, 131t discontinuation prior to surgery, 175, 308 half-life of, 175, 201 interruption of treatment with, 133 lack of antidotes for, 175, 179 measurement of anticoagulant effect of, 132–133 postoperative resumption of, 175 reversal of, 133, 201 as stroke prophylaxis, 308 as venous thromboembolism treatment, 133–135

Dalteparin, use in brain tumor patients, 261

Darbepoetin, 101

D-dimer, 120, 270

D-dimer assay, 28, 35, 122–123, 124, 139, 204

Decision making, patients’ inclusion in, 10

Index

in unusual locations, 137
vasogenic edema in, 194
Deep vein thrombosis prophylaxis adverse effects of, 153–154 indications for brain catheter placement, 376–377, 378–379 cerebrospinal fluid shunt placement, 376–377 craniotomy, 154f, 155–156 elective spinal surgery, 154t, 158 external ventricular drains, 378–379 general guidelines for, 154t in intracranial pressure monitored patients, 378–379 in pediatric patients, 154t, 158–159 spinal cord injury, 154t, 157 traumatic brain injury, 154t, 156–157 Desirudin, 54, 200t, 201 Desmopressin, 55, 56, 75, 77, 387 Desmoteplase, 300 Dextran, 90 Dextrose starches, 90 Dilute thrombin time (DTT), 132 Dipyridamole, 210f Direct factor Xa inhibitors. See Factor Xa inhibitors Direct thrombin inhibitors, 54–55. See also Dabigatran discontinuation of, 201 reversal of, 49t, 55, 76t, 335 unreversibility of, 201 Disseminated intravascular coagulation (DIC), 72, 81, 88 Disseminated intravascular coagulation (DIC) panel, 28, 35, 204 Dura, dissection of, 80 Dural sinuses, 80


Echocardiography, for pulmonary embolism diagnosis, 125, 138 Edoxaban, as intracerebral hemorrhage cause, 346–347, 346f Electrocautery, 72, 73 Embolectomy, open, 298 Embolic agents, 222–225

Index 411
Epstein-Barr virus, transmission in blood transfusions, 88
Eptifibatide, 200t, 203, 213, 300–301
Erythropoiesis-stimulating agents, 101–102, 104
Erythropoietin, 101, 104, 385
Evidence-based medicine (EBM), 3–14
application to preoperative coagulation testing, 26–27
process of, 4t
External carotid artery, preoperative embolization of, 226, 228
External ventricular drains (EVDs), 159, 161, 322, 324, 377–379, 401
Extracranial-intracranial bypass, 299

F
Factor II thrombin inhibitor. See Dabigatran
Factor V deficiency, 43
Factor Leiden, 38, 39t
Factor VII deficiency, 43, 51
Factor VIIa, 77. See also Recombinant factor VIIa
Factor VIII, antibodies against, 43
Factor VIII inhibitors, as hemophilia A treatment, 106
Factor IX deficiency. See Hemophilia B
Factor X, activation of, 19
Factor X deficiency, 43
Factor Xa, inactivation of, 270
Factor Xa inhibitors, 130-131, 131f.
See also Apixaban; Rivaroxaban
classes of, 201
indications for, 49f
lack of antidotes for, 179
measurement of anticoagulant effect of, 132–133
reversal of, 49f, 54, 201
Factor XI, activation of, 19
Factor XIa, 19
Factor XI deficiency, 43
Factor XII, 19
Factor XIII deficiency, 43
Femoral artery, angiography of, 220
Fibrin, 74
Fibrin clots, 270
Fibrin degradation products, 270
preoperative measurement of, 28, 35, 204
Fibrin glue, 242t–243t, 248
Fibrinogen, 19f
preoperative measurement of, 28, 35
Fibrinogen deficiency, 43
Fibrinolysis, 20, 20f, 270
Fibrinolysis inhibitors, 270
Fibrinolytic system, 272f
Filtration, of donated blood, 93, 99–100
Fish oil, 62, 63t, 66
Fistula, arteriovenous, 314
Floseal, 370
Fluid replacement, 90
Fluid status, intraoperative, 89–90
Fluoroscopy, use in embolization, 221–222
Fondaparinux, 128, 200t
Fractures, spinal, 336–337
Fresh frozen plasma (FFP) as coagulation factor replacement, 104–105
collection and storage of, 104
indications for, 92
as vitamin K antagonist reversal agent, 48–50, 51–52, 202
as warfarin reversal agent, 105
in traumatic brain injury, 335, 335f, 338

G
Galen, 241
Garlic (Allium sativum), 62, 63t, 64, 66
Gelatin, as hemostatic agent, 78t, 79t
Gelatin sponges, 242t–243t, 243–244, 245, 251
Gelfoam, 243–244, 245
Ginger, 65, 66
Ginkgo (Ginkgo biloba), 63t, 64–65, 66
Ginseng (Panax ginseng), 63t, 65, 66
Glanzmann thrombasthenia, 42–43
Glasgow Coma Scale scores, in traumatic brain injury patients, 332, 333
Glioblastoma multiforme, 344
Glomus tumors, preoperative embolization of, 228–229
Glycoprotein IIb/IIIa, definition of, 203
Glycoprotein IIb/IIIa inhibitors, 208. See also Abciximab; Eptifibatide; Tirofiban
as bridging therapy, 213
intra-arterial use of, 311
as ischemic stroke treatment, 300–301
resistance to, 313
reversal of, 203
Glycoprotein IIb/IIIa receptors, 74
Glycoprotein receptors, 18
Graft-versus-host disease, 100

H
Halsted, William, 71
Headache, cerebral venous sinus thrombosis-related, 185, 186–187, 186t
Heart valves, mechanical. See Mechanical heart valves
Hemangioblastomas, preoperative embolization of, 227
Hemangiopericytomas, preoperative embolization of, 227
Hematocrit, 72, 81
as intraoperative blood loss indicator, 89, 95
recommended, in surgical patients, 100
Hematomas
at arterial puncture sites, 329, 330
epidural
lumbar drain-related, 379
postoperative, 213–214
spinal, 353, 355–356
venous thromboembolism prophylaxis-related, 153
intracerebral hemorrhage-related, 277–278
retroperitoneal, 337
spinal, 336–337
subdural, 335f
bilateral chronic, 350f, 351
cerebrospinal fluid shunt-related, 377
chronic, 336, 349–351
head fracture-related, 169, 170f
perioperative anticoagulant management in, 214
Hematomyelia, 353
Hemicraniotomy, decompressive, 296–297, 302–303
Hemodialysis, as dabigatran reversal method, 201
Hemodialysis patients, dabigatran use in, 133
Hemodilution
hypervolemic, in pediatric patients, 386–387, 396, 398
normovolemic, 93–94, 96
in pediatric patients, 387
profound, effect on coagulation, 81
Hemoglobin, stroma-free, 104
Hemoglobin levels
effect of red blood cell transfusions on, 100–101
in pediatric patients, 384, 389
recommended, in surgical patients, 100–101
Hemoglobinuria, paroxysmal nocturnal, 41
Hemolytic reactions, to blood transfusions, 88, 100, 107, 108–109
Hemophilia
diagnosis of, 27
in pregnancy, 30
Hemophilia A, 43, 51, 77, 106
Hemophilia B, 43, 51, 77
Hemorrhage
anticoagulants-related, 203–204
antiplatelet agents-related, 203–204
arterial, control of, 72
classification of, 73–74, 81
heparin-related, 127
intracerebral, 277–283, 291
in alcoholic patients, 347–348, 348f
anticoagulant and antiplatelet agent resumption after, 278–281, 284
anticoagulant-related, 274–275, 278, 279
anticoagulant reversal in, 50–51, 277–278
anticoagulation discontinuation-related, 281
Hemorrhage (continued)
antiplatelet agents-related, 282–283
arteriovenous malformation-related, 400–402, 401f
cavernous malformations-related, 277
dabigatran-related catastrophic, 343, 344f
edoxaban-related, 346–347, 346f
recombinant factor VII treatment of, 106
recurrent, antiplatelet drug-related, 283
transfusion goal in, 101
venous thromboembolism prevention and treatment in, 281–282, 284
intracranial anticoagulant-related, 75, 81, 332
anticoagulant reversal in, 314
antiplatelet agents-related, 81
arteriovenous malformation-related, 275–276, 276f
in brain tumor patients, 261–262
deep vein thrombosis prophylaxis-related, 155–156
external ventricular drains-related, 159
perioperative anticoagulant management in, 214
prasugrel-related, 176, 177–178, 177f
stent placement in, 310
in traumatic brain injury patients, 332, 333f
venous thromboembolism prophylaxis-related, 153
as venous thromboembolism risk factor, 120
ventricular catheter-related, 376
warfarin-related, 173, 175
intraparenchymal, 318, 319f, 377, 378
intraventricular, 378
postoperative as epidural hematoma cause, 213–214
preoperative risk assessment of.
See Coagulation testing, preoperative rate of, 172
sagittal sinus thrombosis-related, 344–345, 345f
spinal spontaneous, 353–355
traumatic, 336–337
subarachnoid, 300
acetylsalicyclic acid treatment of, 274
aneurysmal, 322–324
antiplatelet therapy in, 274, 313
dabigatran-related catastrophic, 343, 344f
external ventricular drain placement in, 377–378
hypocapnia in, 90
spontaneous, 291
transfusion goal in, 101
as venous thromboembolism risk factor, 120
Hemostasis
of arterial bleeding, 72
chemical, 241–242, 251
electrical, 241
historical overview of, 71, 241–243
intraoperative, 241–256
during craniotomy, 80
nonhematologic adjuvant, 241–256
laboratory tests of, 21–24, 22f, 23t
mechanical, 242, 251
pharmacological agents for, 75, 77
physiology of, 74
primary, 17
principles of, 81
secondary, 17
thermal, 241, 251
topical agents for, 77, 78t, 82
in vascular injury, 18, 18f
of venous bleeding, 72
Hemostats, 241
Heparin, 301
adverse effects of, 127
in angiographic procedures, 307–309
anticoagulant effect of, 52
as bridge therapy, 172, 209
as cerebral venous sinus thrombosis
treatment, 190
discontinuation prior to surgery,
172, 173, 174r, 376, 377
discovery of, 199
in endovascular venous thrombosis,
328, 329–330
indications for, 52
as intracranial hemorrhage cause,
261–262
low molecular weight
action mechanism of, 200r, 210t
anticoagulant effect of, 210t
as atrial fibrillation prophylaxis,
172
as bridging therapy, 209
as deep vein thrombosis
prophylaxis, 155–157, 158, 159
discontinuation prior to surgery,
210t
half-life of, 210t
postoperative resumption of, 40,
212f
preoperative administration of,
40
reversal of, 49t, 53, 76t, 199, 200t,
201
therapeutic dosage, 210t
use in brain tumor patients,
260–262, 263–264
use in intracerebral hemorrhage,
282
as venous thromboembolism
treatment, 126–128, 134
as warfarin alternative, 331
as warfarin bridging anticoagu-
lation, 211–212
neuroendovascular procedures,
313–314
postoperative resumption of,
172–173, 174t
reversal of, 199–201, 200t, 313–314
in ruptured intracranial aneurysm,
309
as thrombocytopenia cause, 309
unfractionated
action mechanism of, 199, 200t,
210t
adverse effects of, 127–128
anticoagulant effect of, 210t
as deep vein thrombosis
prophylaxis, 155, 156–157, 159
discontinuation prior to surgery,
210t
as epidural hematoma prophy-
laxis, 214
half-life of, 210t
postoperative resumption of, 212f
reversal of, 49t, 52–53, 76t, 199,
200t
therapeutic dosage, 210t
use in intracerebral hemorrhage,
282
as venous thromboembolism
treatment, 126–128, 134
as warfarin bridging anticoagu-
lation, 209, 211–212
use in pregnancy, 121
Heparin pentasaccharide. See also
Fondaparinux
reversal of, 49t, 53–54, 76t, 201
Heparin sulfate, 21f
Hepatitis, as contraindication to
autologous blood donations,
103
Hepatitis screening, of donated blood,
99
Herbal products and supplements,
affecting coagulation, 62–67
Hermansky-Pudlak syndrome, 42–43
Hetastarch, 90
HLA (human leukocyte antigen)
sensitization, 100
Hormone replacement therapy, as
venous thrombosis risk factor,
41
Human immunodeficiency virus
(HIV), transmission in blood
transfusions, 88, 103
Human immunodeficiency virus
(HIV) screening, in blood
donations, 99
Human lymphocytotropic virus
(HTLV), 99
Hydrocephalus
aneurysmal subarachnoid
hemorrhage-related, 378
Chiari 1 malformation-related,
402–404, 403f
Hydrocephalus (continued)
  normal pressure
cerebrospinal fluid shunts in,
  375–377
idiopathic, 348–351, 349f, 350f
pediatric brain tumor-related,
  397–400, 398f
shunt-based diagnosis and
  management of, 377–379
Hypercoagulability, 153
Hypercoagulable states, inherited, 38, 39t
Hyperhomocysteinemia, 39t, 42
Hypertension
  chronic thromboembolic pulmo-
  nary, 118–119
  as intracerebral hemorrhage cause,
    277
  intraoperative, 72
  isolated intracranial, 187
  malignant intracranial, 378–379
  as stroke risk factor, 292
Hyperviscosity, as venous thrombosis
  risk factor, 42
Hypotension
  controlled, 72
  deliberate, in pediatric patients, 387
  volume depletion-related, 89
Hypothermia, effect on platelet
  function, 81
Hypovolemia
  in pediatric patients, 384
  signs of, 89

I
Idraparinux, 201
Iliac vein, deep vein thrombosis of,
  137
Immobilization, as venous thrombosis
  risk factor, 41
Immunocompromised patients
  blood transfusions in, 89
  graft-versus-host disease in, 100
Immunosuppression, blood
  transfusion-related, 89
Infants
  craniosynostosis in, 395–397, 396f
  hemoglobin levels in, 384, 389
Infectious diseases, transmission in
  blood transfusions, 88, 99
Infectious disease screening, of
  donated blood, 99
Inferior vena cava filters
  in brain tumor patients, 263–264
  versus bridging anticoagulant
    therapy, 214
  complications of, 159–160
  indications for, 282
  in neurosurgery patients, 136, 160,
    161, 162
  in neurotrauma/polytrauma
    patients, 161
  in spine reconstruction patients,
    160
  in venous thromboembolism, 135,
    139
Internal carotid artery, angiography
  of, 220
International normalized ratio (INR),
  27, 35, 95
  intensity of, 129
  of vitamin K antagonists, 48, 49t
Intracranial pressure elevation,
  cerebral venous sinus
  thrombosis-related, 191
Intracranial pressure monitors,
  377–379
Iron supplementation, in pediatric
  patients, 385, 397
Irradiation, of blood products, 100
Ivy method, of bleeding time
  assessment, 87

J
Jehovah’s Witnesses, blood replace-
  ment in, 94–95, 103–104

K
Kallikrein, 19

L
Lacunar disease, 292
Lacunar syndrome, 293
Large-artery disease, 292
Lasers, use in neurosurgery, 250–251
Lepirudin, 54, 200t, 201
Leukodepletion, of donated blood,
  99–100
Ligatures, 72, 73
Liver disease, 42, 43
Lumbar drains, 379–380
Lumbar puncture, 380

Magnetic resonance imaging, of pulmonary embolism, 125
Malignant middle cerebral artery syndrome, 291, 295–296, 302–303
McLean, Jay, 199
Mechanical heart valves
  anticoagulant management with, 173, 174, 278–279, 280–281
  as thromboembolism risk factor, 279, 279f
Mechanical thrombus fragmentation, 135
Meningiomas, preoperative embolization of, 226
Mesenteric veins, deep vein thrombosis of, 137
Metastatic spine disease, preoperative embolization of, 230–231
Middle cerebral artery syndrome. See Malignant middle cerebral artery syndrome
Middle meningeal artery, preoperative embolization of, 226, 228
Myeloproliferative neoplasms, as venous thrombosis risk factor, 41
Myocardial infarction, stent thrombosis-related, 169

Nafamostat, 77
Nephrotic syndrome, as venous thrombosis risk factor, 41
Nerve injury, traumatic, 337–338
Neuroendovascular procedures, anticoagulant/antiplatelet agent management in, 307–317
  as deep vein thrombosis prophylaxis, 159
  as ischemic stroke treatment, 298
  patient/case examples of, 318–330
Neuropathy, compressive, 337
Neurovascular lesions, anticoagulant and antiplatelet agent risk management in, 272–284
cavernous malformations, 276–277
intracerebral hemorrhage, 277–283
unruptured arteriovenous malformations, 275–276
unruptured intracranial aneurysms, 272–275
Nonsteroidal anti-inflammatory drugs (NSAIDs), 208. See also Acetylsalicylic acid (ASA); Aspirin
  antiplatelet activity of, 332
Number needed to harm (NNH), 9
Number needed to treat (NNT), 9

Octaplex, 106
1:1 mixing study, 28
Onyx, 223, 224, 225, 226, 227, 228, 229, 231, 232
Ophthalmoplegia, cerebral sinus venous thrombosis-related, 188
Oral contraceptives, as venous thrombosis risk factor, 41
Ostene, 78
Osteoporosis, heparin-related, 127, 128
Oxicel, 242–243

Packed red blood cells (pRBCs), 90–91
Paragangliomas, preoperative embolization of, 228–229
Paré, Ambroise, 241
Partial anterior circulation syndrome (PACS), 293
Partial thromboplastin time (PTT). See also Activated partial thromboplastin time
  in angiographic procedures, 307
  definition of, 86
  preoperative measurement of, 27, 85, 86
  prolonged, 32, 33t, 34f
Partial thromboplastin time (PTT) assay, 22, 22f
in bleeding disorders, 22, 23t, 24
Particle embolics, 222–223
Pediatric neurosurgery, blood loss prevention and treatment in,
384–394
intraoperative strategies for,
386–389, 390
patient/case examples of, 395–404
preoperative strategies for,
385–386, 389
Pentasaccharides. See Heparin pentasaccharide
Peripheral vascular disease, warfarin anticoagulation in, 208
Phenprocoumon, 200t, 201
Plasma components, 104–106
Plasma protein fraction, 90
Plasminogen activator inhibitor, 20f, 270
Platelet(s), physiology and function of,
17–18
Platelet aggregation studies, preoperative, 29
Platelet count, 21
in bleeding disorders, 23t
in cranial surgery patients, 92
effect of platelet transfusions on,
91, 96
normal, 86
preoperative assessment of, 26, 27,
35, 85, 86
relationship to platelet function,
86, 95
in thrombocytopenia, 102, 204
Platelet disorders
acquired, 42
inherited, 42–43
Platelet donations, 100
Platelet function
preoperative assessment of, 87
regulatory mechanisms of, 20, 21f
tests of, 21
Platelet function analyzer (PFA-100),
29, 202–203
Platelet transfusions, 102
for antiplatelet agent reversal, 76f
effect on platelet count, 96
prophylactic, 91–92
in thrombocytopenia, 91
in traumatic brain injury, 335, 338
Plavix. See Clopidogrel
Polyvinyl alcohol (PVA) particles, as embolic agents, 223, 226, 227,
228, 229
Popliteal vein, thrombosis of, 117
Posterior circulation syndrome (POCS), 293
Posterior inferior cerebellar artery, occlusion of, 297–298
Postthrombotic syndrome, 118, 125,
138, 159–160
Prasugrel
action mechanism of, 56, 176, 200t
adverse effects of, 176, 177–178,
177f
antiplatelet activity of, 56, 203
comparison with clopidogrel, 176
discontinuation prior to surgery,
177, 179
half-life of, 56, 176
reversal of, 56, 57, 200t, 203
Pregnancy
cerebral venous sinus thrombosis in, 184, 185, 189
iliac vein thrombosis in, 137
partial thromboplastin time in, 30
venous thromboembolism in, 40,
121
Prekallikrein, 19
Procrit, 385
Protamine/protamine sulfate, as heparin reversal agent, 49t,
52–53, 76t, 199, 200t, 201
Protein C
activation of, 20, 270
warfarin-related inhibition of, 128
Protein C coagulation pathway, 20
Protein C deficiency, 39t
Protein S
activation of, 270
warfarin-related inhibition of, 128
Protein S deficiency, 39t
Prothrombin complex concentrates (PCCs)
adverse effects of, 106
as direct thrombin inhibitor reversal agents, 55
four-factor, 75
as hemophilia B treatment, 105
as intracerebral hemorrhage treatment, 105–106
preparation of, 105
three-factor, 75
as vitamin K antagonist reversal agents, 48–49, 50–51, 55, 75, 202, 335, 335f
as warfarin reversal agent, in traumatic brain injury, 335, 335f
Prothrombin deficiency, 43
Prothrombin gene mutations, 38, 39t
Prothrombin time (PT)
in angiographic procedures, 307–308
definition of, 86
international normalized ratio (INR) format of, 27, 35, 86
preoperative measurement of, 26, 27, 35, 85, 86, 204
prolonged, 269–270, 284
Prothrombin time (PT) assay, 22, 22f in bleeding disorders, 22, 24
Pseudoaneurysms, stenting of, 324, 325f
PTT. See Partial thromboplastin time (PTT)
Purpura, thrombocytopenic chronic idiopathic, 348–349, 349f
P2Y12 antagonists, 176–178. See also Prasugrel

Q
Quebec platelet disorder, 42–43

R
Randomized clinical trials (RCTs), 5–7, 7t–8t, 26–27
Recombinant factor VIIa, as intracerebral hemorrhage treatment, 106
Recombinant factor VIIa, 202, 388
as thromboembolism cause, 202
use in pediatric patients, 388
as vitamin K antagonist reversal agent, 48–49, 51–52, 202
Red blood cells, storage of, 99
Red blood cell savers. See Cell savers
Red blood cell transfusions. See Cell savers
Regional anesthesia, adverse effects of, 337–338
Renal cell carcinoma, metastatic, 230, 259
Renal disease, as venous thrombosis risk factor, 41
Renal transplantation, as venous thrombosis risk factor, 41
Rh blood type, 87
of donated blood, 99
Risk-benefit ratios, 9
Rivaroxaban, 54, 55, 130–131, 131t action mechanism of, 176
discontinuation prior to surgery, 176
effect on prothrombin time, 201
efficacy of, 176
half-life of, 176
interruption of treatment with, 133
postoperative resumption of, 176
reversal of, 133, 201
as venous thromboembolism treatment, 133–135

S
Sagittal imbalance, fixed, 368–371, 369f
Saline solutions, 90
Scalp, blood loss control in, 80
Scoliosis surgery, 94, 386–387, 387
Scott's syndrome, 43
Seizures, cerebral venous sinus thrombosis-related, 187, 187t, 191
Serine proteases, 74–75
Shunts, ventriculoperitoneal, 351, 375–377
Smoking, as intracerebral hemorrhage risk factor, 280
Spinal cord injury
acute cervical, 372–373, 372f, 373f
anticoagulant/antiplatelet agent use in
for deep vein thrombosis prophylaxis, 154f, 157, 161
as spontaneous spinal hemorrhage cause, 354–355
Spinal cord injury (continued)
perioperative spinal hemorrhage in, 359–360
as venous thromboembolism risk factor, 120, 161, 359
Spinal deformity, 368–371, 369f
Spinal disorders, anticoagulant and antiplatelet therapies in, 354–355
Spinal tumors, 230–231, 354
Spine surgery patients, 353–366, 356
blood replacement in, 93
bridging anticoagulation in, 214
deep vein thrombosis prophylaxis in, 154t, 158
perioperative spinal hemorrhage risk in, 356–357
as spontaneous spinal hemorrhage cause, 354–355
venous thromboembolism prophylaxis in, 357–358
patient/case examples of, 367–374
in reconstructive surgery, 160
venous thromboembolism risk in, 120, 355–356, 359
Splanchnic veins, deep vein thrombosis of, 137
Stenosis, spinal, 367–368, 369f
Stents/stenting
of aneurysms, 309, 315, 320–322, 321f, 378, 379
anticoagulation therapy with, 309–310
antiplatelet therapy discontinuation prior to, 213
antiplatelet therapy with, 309, 315
cardiac, 168–169, 170f, 172f, 177–178, 178–179
carotid, 299, 309, 324–326, 325f
coronary, 264, 368, 370–371
restenosis of, 315
retrievable, as mechanical thrombectomy, 326–328, 327f
thrombus formation in, 320–322, 321f
Storage pool diseases, 42–43
Streptokinase, 300

Stroke
antiplatelet agent prophylaxis for, 273
arteriovenous malformation-related, 307
aspirin prophylaxis of, 167
atrial fibrillation-related, 170–172, 171f
cardioembolic, 292
cerebral venous sinus thrombosis-related, 193
coil embolization-related, 322
cryptogenic, 291–292
definition of, 291, 302
endovascular revascularization in, 310–311
first-ever, 291
heparin use in, 314
ischemic
acute medical treatment of, 295–300
atrial fibrillation-related, 279–280, 279t
clinical syndromes of, 293
complications of, 296
definition of, 291
diagnosis of, 293–295, 294t
embolization-related, 228
epidemiology of, 291–292, 302
imaging in, 293, 295, 295f, 296f
perioperative, 299
pharmacological treatment of, 300–301
tissue plasminogen activator treatment for, 326, 327–328
unruptured aneurysm associated with, 275
mechanical heart valves-related, 279
neuroendovascular procedures in, 310–311
prevalence of, 291
as venous thromboembolism risk factor, 120–121
Stypics, 241
Superficial vein thrombosis (SVT), 137
Surgery, as venous thrombosis risk factor, 40
Surgicel, 242t–243t, 244–246
Surgifoam, 243
Syringomyelia, 402–404, 403f

T
Tachycardia, blood loss-related, 73, 81, 89
Tenectoplace, 300
Thienopyridines, 56. See also Clopidogrel; Prasugrel
discontinuation of, in coronary stent patients, 168–169
reversal of, 203
Thrombectomy, 311, 326–328, 327f
Thrombin, 74
activation of, 271f
as hemostatic agent, 79t, 242t–243t, 247, 251
inactivation of, 270
production of, 19, 19f
role in coagulation, 270
Thrombin-activatable fibrinolysis inhibitor, 270
Thrombin time (TT), preoperative measurement of, 27–28
Thrombocytopenia
artifactual, 86
differential diagnosis of, 86
heparin-related, 127–128, 309
platelet transfusions for, 102
preoperative assessment of, 28
Thrombocytosis, preoperative assessment of, 28
Thromboelastography, 29
Thromboembolism. See also Venous thromboembolism
embolization-related, 314–315
mechanical heart valves-related, 279, 279t
neuroendovascular procedure-related, 307
recombinant factor VIIa-related, 202
Thrombolysis
catheter-directed, 135
directional venous, 190, 311–312, 328–330, 329f
as stroke treatment, 295
Thrombomodulin, 270
Thrombophilia
inherited, 38, 39t, 43
during pregnancy, 121
Thromboprophylaxis, 40
Thrombosis. See also Deep vein thrombosis (DVT)
definition of, 38
prothrombin complex concentrates-related, 106
venous sinus, 291
Thromboxane A2, 74
aspirin-related inhibition of, 202
Thrombus formation
on aneurysm embolization coils, 312–313, 320–322, 321f
on endovascular catheters and wires, 308, 312–313
Thyroid carcinoma, metastatic, 230, 259
Ticlopidine, 76, 76t
Tirofiban, 208, 213
Tissue factor, 19, 19f, 86, 271f
Tissue factor pathway inhibitor, 19f, 20, 270
Tissue plasminogen activator, 20, 20f, 295
in endovascular procedures, 310–311, 313
intra-arterial use of, 311
as ischemic stroke treatment, 326, 327–328
postoperative use of, 314
as venous thrombosis treatment, 311–312
Total anterior circulation syndrome (TACS), 293
Tranexamic acid, 77, 270, 322, 323, 370, 371
use in pediatric patients, 387, 398
Transfusion reactions. See Blood products, adverse reactions to
Transient ischemic stroke, 291
Trauma
inferior vena cava filter use in, 161
as venous thromboembolism risk factor, 40, 120
Trauma patients, anticoagulants and antiplatelet agents use in,
331–342
Traumatic brain injury, anticoagulant and antiplatelet use in, 331
in alcoholic patients, 347–348, 348f
as deep vein thrombosis prophylaxis, 154t, 156–157, 161
management guidelines for, 334–335, 334f, 335f
preinjury use, 332–333, 333f
resumption after injury, 336–338
Troponin, 123, 125

U
Ultrafiltration, of whole blood, 93
Ultrasonography, for deep vein thrombosis diagnosis, 123–124
Upper extremities, deep vein thrombosis of, 137
Urine output, as hypovolemia indicator, 89

V
Vascular malformations, spinal, 354–355
Vasoconstriction, blood loss-related, 73, 81
Vena cava filters. See Inferior vena cava filters
Venography, 124, 328, 329f
Venous bleeding, control of, 72
Venous thromboembolism, 117–152
acquired, causes of, 39–42
anticoagulant reversal-related, 204
anticoagulant therapy for, 125–135, 138–139
adverse effects of, 127, 129
long-term, 128–129, 130
with new anticoagulants, 130–135
over-anticoagulation management in, 129–130
for recurrent venous thromboembolism, 129
temporary interruption of, 130, 133
antiplatelet agent reversal-related, 204
in brain tumor patients, 263–264
definition of, 117, 153
diagnosis of, 121–125, 138
etiology and pathogenesis of, 38–42, 119
incidence of, 117–118
inherited, 38, 39t
in pediatric patients, 384, 389
perioperative, risk stratification for, 209, 211, 211t
prophylaxis against, 118, 281–282, 284, 357–358
risk factors for, 119–121, 138, 153
serious consequences of, 118–119, 138
sinus. See Cerebral venous sinus thrombosis
spinal injury-related, 359
spinal neoplasm-related, 354
treatment of, 125–137, 139
with catheter-directed thrombolysis, 135, 139
endovascular, 311–312
with inferior vena cava filter, 135, 139
in intracerebral hemorrhage, 282
with mechanical thrombus fragmentation, 135
in neurosurgery patients, 136–137, 139
warfarin anticoagulation therapy for, 208
Venous thromboembolism prophylaxis, 153–166
in brain tumor patients, 260–263
chemical, 154, 154t, 155, 360–362
mechanical, 153–154, 154t, 155, 360, 361
in spinal injury patients, 359–362
in spinal surgery patients, 368, 370, 371, 373
Ventilation/perfusion (V/Q) lung scanning, 124–125
Ventriculomegaly, 348–349, 349f
Vertebral artery, traumatic injury to, 299–300, 303
Viral disease screening, of donated blood, 99
Virchow’s triad, 38, 153
Vitamin E, 63t, 65, 66
Vitamin K, as vitamin K antagonist reversal agent, 48–49, 52, 75, 76t, 202
Vitamin K antagonists, 47, 75. See also Warfarin
as cerebral venous sinus thrombosis treatment, 190–191
discovery of, 201
half-lives of, 201–202
reversal of, 48–49, 49t, 75, 76t, 202, 301
as venous thromboembolism treatment, 136
Vitamin K deficiency, as coagulopathy cause, 43
Vitamin K-dependent clotting factor inhibitors. See also Warfarin
Volume replacement, 89–90
von Willebrand disease, 30, 42–43
von Willebrand factor, 17
von Willebrand factor receptor, 17
von Willebrand panel, 28

W
Wallenberg syndrome, 297
Warfarin
action mechanism of, 200t, 201, 210t
adverse effects of, 173, 175
anticoagulant effect of, 210t
as atrial fibrillation prophylaxis, 170, 172
in cardiovascular disease patients, 174f
discontinuation prior to surgery, 210t, 377
bridging anticoagulation for, 172, 174t, 209, 211–212, 212f
half-life of, 210t
indications for, 208–209
international normalized ratio (INR) of, 128–128, 212–213
as intracerebral hemorrhage cause, 201
as intracranial hemorrhage cause, 274, 332
metabolism of, 331
postoperative resumption of, 212–213
reversal of, 47–52, 48, 49t, 76t, 92, 308, 335, 338
teratogenicity of, 121
therapeutic dosage of, 210t
therapeutic monitoring of, 331
as venous thromboembolism treatment, 128–129, 134, 263
West Nile virus, 99
Wiskott–Aldrich syndrome, 43