Optimizing the Selection and Use Of Topical Hemostats

This monograph is based on a symposium held in Boston on November 12, 2011.

Participant online at topical-hemostats.com

Release Date: April 1, 2012
Expiration Date: April 1, 2013

Statement of Need
Intraoperative hemostasis is an important clinical goal; excessive bleeding is associated with prolonged procedures, extended hospitalization, and serious complications. Low clinician awareness has been observed around the availability, selection, and use of the array of topical hemostats. Educational and knowledge gaps also are acknowledged by pharmacists with regard to the use of topical hemostats, as these products may enter hospitals via central supply rather than pharmacy ordering. Topical hemostats have diverse clinical and pharmacoeconomic profiles, and a number of direct and non-medication costs (eg, storage, preparation, product waste, potential for uncommon but serious side effects) must be considered with their use.

Program Goal
To educate clinicians on the selection and use of topical hemostats in the hospital setting.

Learning Objectives
After completing this activity, participants should be better able to:

- Appraise the clinical and economic effects of excessive intraoperative or postoperative bleeding and common preoperative strategies for minimizing bleeding events.
- Describe key clinical factors that influence the selection and use of topical hemostats as adjuncts for achieving surgical hemostasis.
- Delineate clinical characteristics and pharmacoeconomic (direct and non-medication costs) considerations by which topical hemostats should be evaluated, acquired, and used in hospitals.
- Develop a plan for reconciling cautionary guidance and clinical best practices with regard to the selection and use of the full range of topical hemostats.

Target Audience
This activity is designed to meet the educational needs of physicians, pharmacists, nurses, and other health care professionals.

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Dr. Doria: Nothing to disclose
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Estimated Time of Completion: 120 minutes.

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Chair
Cataldo Doria, MD, PhD, FACS
Nicetelli Family Professor of Transplant Surgery
Director, Division of Transplantation
Co-Director, Jefferson Kimmel Cancer Center – Liver Tumor Center
Thomas Jefferson University Hospital
Philadelphia, Pennsylvania

Faculty
Danial E. Baker, PharmD
Professor of Pharmacotherapy
Associate Dean for Clinical Programs
Director, Drug Information Center
College of Pharmacy
Washington State University
Spokane, Washington

Bradley A. Boucher, PharmD, FCCP, FCCM
Professor, Vice-Chair for Institutional Programs
Department of Clinical Pharmacy
Associate Professor
Department of Neurosurgery
University of Tennessee Health Science Center
Memphis, Tennessee

Medical Writer
Mary Culpepper

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Introduction

Despite advances in surgical techniques and operative hemostasis management, excessive bleeding remains a major surgical complication that contributes to poor clinical outcomes. Excessive blood loss has been reported in 3% to 14% of cardiovascular surgeries, and re-exploration for microvascular bleeding after cardiac surgery is an important source of morbidity and mortality. In one study, mortality rates increased from 8% in patients who lost less than 500 mL of blood during surgery to 42.9% for those who lost more than 2,000 mL. This requires maintenance of a fine balance between bleeding and clotting risks, a challenge that is intensified by the use of potent antithrombotic drugs. These risks extend beyond surgery; although the hemostatic pendulum swings toward bleeding intraoperatively, it moves toward clotting immediately postoperatively and back toward bleeding in recovery. Surgeons must anticipate and manage bleeding.

Adjuncts to intraoperative hemostasis such as hemostats, sealants, and adhesives represent an increasingly important approach to controlling perioperative bleeding, particularly for minimally invasive operations in which bleeding may not be amenable to conventional methods of hemostasis (ie, suture, ligature, cautery). Optimal selection and use of these agents requires surgical team members—surgeons, anesthesiologists, hematologists, pharmacists, and nurses—to understand the available materials and products in order to arrest bleeding intraoperatively and minimize risk for adverse events (AEs) postoperatively.

Among adjunct products are topical thrombins, which have been used successfully as hemostats since the 1940s and currently are used in more than 1 million US surgeries annually. However, bovine-derived topical thrombin preparations occasionally have been associated with hemostatic abnormalities ranging from asymptomatic to mild or severe bleeding or thrombosis, which rarely have been fatal. Believed to be uncommon, immune-mediated coagulopathies (IMCs) result from the development of antibodies that cross-react with human coagulation factors and disrupt inherent clotting mechanisms. Topical thrombins of 3 biologic origins are available, with 2 introduced since 2007. Clinical concerns associated with each are appropriate for review, given their prevalence as standalone hemostats and in combination with other adjuncts to surgical hemostasis.

Minimizing Perioperative Bleeding

Strategies for reducing excessive bleeding are multimodal and can be initiated before, during, and after surgery (Table 1). Among others, medications that irreversibly inhibit the P2Y12 platelet receptor should be discontinued; the potentially lethal triad of coagulopathy, hypothermia, and acidosis should be corrected, and minimally invasive techniques used. When conventional methods are inadequate to control mild to moderate bleeding, or for bleeding that may not be amenable to those approaches (eg, diffuse raw surface bleeding, friable tissue, bone bleeding), topical hemostats represent a reasonable adjunct approach. They are not substitutes for meticulous surgical technique, and their effectiveness depends on appropriate selection and application.

Despite the improved safety of the blood supply, the importance of limiting transfusion is recognized (sidebar, Rationales for Restrictive Transfusion Strategies).

Coagulation and Hemostasis

Coagulation is a physiologic defense mechanism that maintains circulatory integrity and limits blood loss after a vascular insult. The generation of thrombin from its precursor, prothrombin, is the central event of coagulation—a process that is central to physiologic hemostasis, implicated in thrombosis, and dependent on a complex sequence of self-activating biochemical reactions among circulating coagulation factors. Traditionally, hemostasis has been described as a cascade of enzymatic reactions occurring on cell surfaces containing exposed tissue factor and phospholipids resulting in the formation of thrombin (IIa), a serine protease. The process of coagulation itself is one of vasoconstriction, platelet plug formation, cross-linking of fibrin, and fibrinolysis (ie, clot dissolution).

Thrombin controls the final step of the coagulation cascade by catalyzing the conversion of soluble fibrinogen to fibrin to form the basis of a blood clot; inducing cross-linking of the fibrin clot through factor XIII activation; and activating platelets—ultimately forming a stable, cross-linked, fibrin–platelet clot. In addition, coagulation activity is amplified via platelet-mediated thrombin generation (ie, thrombin bursts) and activation of factors V, VIII, and XI. Thrombin, which also binds to specific receptors, enhancing platelet aggregation, is a multifaceted biological mediator with both procoagulant and anticoagulant functions, among others.

In surgery, thrombin products are used as biologically active hemostats to convert fibrinogen to fibrin at the site of active bleeding.
Rationale for Restrictive Transfusion Strategies

As a result of screening improvements, the safety of the US blood supply has increased dramatically; rates of transfusion-transmitted HIV and hepatitis C and B viruses are 1 in 2,135,000; 1 in 1,935,000, and 1 in 205,000 transfusions, respectively. The majority of transfusion-related morbidity and mortality now is caused by noninfectious complications, such as transfusion-associated acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and hemolytic transfusion reactions (associated with ABO or non-ABO alloantibodies) resulting from incorrect blood component transfusion (ie, mis-transfusion). Blood transfusions also have been associated with dose-responsive increases in multiorgan failure in trauma patients and increased mortality in critically ill patients. Although the blood supply is the safest it has ever been, there is a growing appreciation that unnecessary transfusions are not prudent in view of the potential harm from a variety of serious complications and that the safest transfusion is no transfusion.

In the coagulation cascade, circulating prothrombin is converted to active thrombin by activated factors X and V. The conventional model (Figure 1) is represented as 2 somewhat independent pathways (ie, extrinsic, intrinsic) that converge at the point in which factor V is situated; thrombin generation can be disrupted profoundly by any substance or event that inhibits factor V. Because some components of physiologic hemostasis were not represented fully by the cascade, a cell-based model has been developed. In these models, coagulation properties are localized to specific cell surfaces, and thrombin plays central roles in 3 overlapping phases: initiation, amplification (ie, activation of factors V and XI, cleavage of factor XIII); and propagation that ultimately results in clot formation.

The cascade model has proven useful in characterizing pathways that reflect the processes measured in the clinical coagulation laboratory. When possible, patients should be risk-stratified preoperatively for bleeding or thrombosis, with careful attention given to history of previous bleeding and use of medications that affect that clotting (Table 2). Based on levels of concern, screening laboratory tests of coagulation (eg, activated partial thromboplastin time [aPTT], prothrombin time [PT]) may be ordered. Surgical teams also can use point-of-care tests for the measurement of activated clotting time (ACT), aPTT, and PT to guide anticoagulation therapy intraoperatively; one such test, thromboelastography, evaluates a broad spectrum of the coagulation cascade.
Bleeding in the Surgical Patient

Bleeding is expected in most surgical procedures and may be anticipated in some that are considered nonsurgical (eg, percutaneous coronary intervention). Multiple factors may account for blood loss in procedures with particularly high bleeding risks, such as cardiopulmonary bypass (CPB), and joint or spine orthopedic surgery; a constellation or series of events or “multiple hits” may be responsible, in conjunction with isolated or multiple hemostatic defects. For example, surgery induces a hyperadrenergic state, causing the release of tissue plasminogen activator (TPA) and consumption of coagulation factors, platelets, and physiologic anticoagulants secondary to bleeding and hemodilution.

In cardiac and liver surgeries, approximately 75% to 90% of bleeding is caused by local surgical interruption or vessel interruption, with 10% to 25% resulting from acquired or congenital coagulopathy. CPB with extracorporeal circulation disrupts hemostasis in several ways: hemodilution, activation of tissue factor and fibrinolysis, consumption of thrombin and plasmin, the release of other inflammatory-mediated factors, and consumption of clotting factors. Also contributing to bleeding in CPB are patient factors (eg, advanced age, emergency surgery, long duration of extracorporeal circulation). Spinal orthopedic surgeries may be associated with major and prolonged bleeding as well, a consequence of long surgery duration, muscle dissection, bone excision, and disruption of internal vertebral vessels. Other surgical procedures with high bleeding risks include joint orthopedic surgery (eg, hip or knee arthroplasty), hysterectomy, vascular grafting, colorectal surgery, and craniotomy. Different surgery types have different effects on the coagulation system, necessitating individualized treatment strategies.

The volume of intraoperative blood loss varies widely by procedure and institution and may be affected by the type and delivery of anesthesia and degree of hypotension. Severe bleeding often is defined as greater than 2 L of blood loss within the first 24 hours postoperatively, representing approximately 40% of circulating blood volume in an adult of average size. Although overall mortality in elective and urgent surgery is very low (0.1%), it can be much higher in specific subcategories, reaching 20% in elective vascular surgery with severe bleeding and 40% in cases of major organ damage (eg, liver rupture).

Spectrum of Agents To Aid Hemostasis

Functional characteristics, mechanisms, and materials are important considerations in the selection of an adjunct to hemostasis, as are patient factors, surgery type, and the characteristics of the bleeding encountered. Three main groups of agents are FDA-approved to aid in topical hemostasis.

Sealants polymerize, activate, and form a mechanical barrier to leakage, with or without the presence of blood. They can prevent the leakage of blood (ie, vascular sealing) as well as nonclotting fluids (eg, dural sealing to prevent cerebrospinal fluid loss). Adhesives fully polymerize, activate, and join tissues and are used externally in combination with deep dermal sutures to facilitate skin closure. They function without need for an intact clotting mechanism; some cyanoacrylate-based adhesives act as barriers against bacteria penetration as well.

Topical hemostats, which promote blood clot formation directly, are among the most widely used intraoperative bleeding interventions. Because of their effectiveness and ease of use, topical hemostats often are surgeons’ first choices for controlling bleeding. Also, although direct acquisition costs vary by hospital, topical hemostats are relatively inexpensive compared with sealants and adhesives. Some are more difficult than others to store, prepare, and use, and these considerations may have clinical and pharmacoeconomic

| Table 2. Preoperative Hemostatic Evaluation\(^\text{11}\) |
|---|---|---|
| **Risk Level** | **History/Physical** | **Tests** |
| **Level 1** | Negative history, physical examination | None required |
| | Minor procedure |  |
| **Level 2** | Negative history, physical examination | aPTT, platelet count |
| | Major procedure |  |
| **Level 3** | Suspicious history | aPTT, platelet count, PT, BT |
| | Procedure with high risk for bleeding |  |
| **Level 4** | History strongly suggestive of major hemostatic defect | BT after aspirin to rule out vWD; specific assays for factors VIII and IX; thrombin time |

aPTT, activated partial thromboplastin time; BT, bleeding time; PT, prothrombin time; vWD, von Willebrand disease
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| Table 3. Topical Hemostats\(^\text{30}\) |
|---|---|---|---|
| **Use** | **Ease of Preparation, Use** | **Cost** | **Examples** |
| Mechanical | Minimal bleeding | Relatively easy | Relatively inexpensive | Gelatin
Collagen
Oxidized regenerated cellulose
Polysaccharide spheres |
| Active | Localized, diffuse bleeding | Relatively easy | More expensive than mechanical; less expensive than flowable, fibrin sealant | Topical thrombins of 3 biologic origins
• Bovine
• Pooled human plasma
• Recombinant |
| Flowable | Localized bleeding | Relatively easy | More expensive than mechanical, active | Gelatin granules + thrombin |
| Fibrin sealant | Localized, diffuse bleeding | Relatively more complex | More expensive than mechanical, active, flowable | Fibrinogen + thrombin |
implications affecting which are purchased by a hospital.

Topical hemostats are subcategorized as mechanical, active, flowable, and fibrin sealants (fibrin sealant is unique in that it has separate FDA approvals as a hemostat, sealant, and adhesive) (Table 3). Mechanical hemostats (Table 4) promote clotting by acting as a barrier to blood flow and creating a scaffolding on which clotting can occur. They can be used immediately out of the package, are applied to a bleeding site using direct pressure, and are most useful

<table>
<thead>
<tr>
<th>Table 4. Mechanical Agents</th>
<th>Clinical Considerations</th>
<th>Risks, Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcine gelatin</td>
<td>Sponge and powder</td>
<td>Sponge and powder</td>
</tr>
<tr>
<td>• Gelfoam absorbable gelatin sponge,</td>
<td>Store at RT</td>
<td>Store at RT</td>
</tr>
<tr>
<td>• compressed sponge,</td>
<td>Immediately available for use</td>
<td>Immediately available for use</td>
</tr>
<tr>
<td>• powder</td>
<td>Not resterilizable</td>
<td>Not resterilizable</td>
</tr>
<tr>
<td>• Surgifoam absorbable gelatin sponge,</td>
<td>Use alone or + saline/topical thrombin</td>
<td>Use alone or + saline/topical thrombin</td>
</tr>
<tr>
<td>• powder</td>
<td>When possible, remove after hemostasis</td>
<td>When possible, remove after hemostasis</td>
</tr>
<tr>
<td>Bovine collagen</td>
<td>Single or multiple sheets</td>
<td>Single or multiple sheets</td>
</tr>
<tr>
<td>• Avitene Ultrafoam collagen sponge,</td>
<td>Store at RT</td>
<td>Swelling; infection</td>
</tr>
<tr>
<td>• flour, sheets</td>
<td>Immediately available for use</td>
<td>(relatively safe)</td>
</tr>
<tr>
<td>• Instat, Instat MCH</td>
<td>Not resterilizable</td>
<td></td>
</tr>
<tr>
<td>• Use dry (not + thrombin)</td>
<td>Use dry (not + thrombin)</td>
<td></td>
</tr>
<tr>
<td>• Remove excess</td>
<td>Remove excess</td>
<td></td>
</tr>
<tr>
<td>Oxidized regenerated cellulose</td>
<td>Sheets, flours, sponges</td>
<td></td>
</tr>
<tr>
<td>• Surgical, Surgical Fibrillar, Surgical Nu-Knit, Surgical Snow</td>
<td>Store at RT</td>
<td></td>
</tr>
<tr>
<td>• Powder in bellows applicator</td>
<td>Avoid extreme temperatures (&lt;–40ºF and &gt;140ºF)</td>
<td></td>
</tr>
<tr>
<td>• Immediately available for use</td>
<td>Not resterilizable</td>
<td></td>
</tr>
<tr>
<td>• Use dry (not + saline/thrombin)</td>
<td>Remove excess</td>
<td></td>
</tr>
<tr>
<td>• Remove excess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polysaccharide spheres</td>
<td>RT, room temperature</td>
<td></td>
</tr>
<tr>
<td>• Arista AH, Hemostase MPH, Vitasure</td>
<td>A kit (Gelfoam Plus) also is available: porcine gelatin sponge + 125 IU/mL lyophilized human pooled thrombin; does not require refrigeration.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. Active Hemostats (Topical Thrombin)</th>
<th>How Supplied</th>
<th>Storage</th>
<th>Risks, Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic Origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine</td>
<td>Powder for solution, 5,000-IU vial, 5-mL diluent</td>
<td>2°C-25°C unopened</td>
<td>Black box warning Do not inject Do not use for massive or brisk arterial bleeding Antibody formation, hemostatic abnormalities Hypersensitivity to material of bovine origin</td>
</tr>
<tr>
<td>• Thrombin-JMI14</td>
<td>20,000-IU vial, 20-mL diluent</td>
<td>2°C-8°C for ≤24 h after reconstitution RT for ≤8 h after reconstitution</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>Frozen solution, 2-, 5-, 20-mL vials (800-1,200 units/mL)</td>
<td>Frozen (≤–18°C) for ≤2 y 2°C-8°C for ≤30 d unopened RT for ≤24 h</td>
<td>Do not inject Do not use for massive or brisk arterial bleeding Risk for plasma-derived infectious disease Anaphylactic or severe systemic reaction to human blood products</td>
</tr>
<tr>
<td>• Evithrom49</td>
<td>Device kit containing lyophilized powder for reconstitution, use with gelatin sponge</td>
<td>2°C-25°C unopened 2°C-25°C for ≤24 h after reconstitution</td>
<td>Do not inject Do not use for massive or brisk arterial bleeding Hypersensitivity to hamster or snake proteins</td>
</tr>
</tbody>
</table>

| Recombinant                                 | Powder for solution, 5,000-IU vial, 5-mL prefilled diluent syringe, 5-mL empty syringe, preprinted label | 2°C-25°C unopened 2°C-25°C for ≤24 h after reconstitution | Do not inject Do not use for massive or brisk arterial bleeding Hypersensitivity to hamster or snake proteins |
| • Recothrom50                               | 20,000-IU vial, 20-mL diluent syringe with 2 sterile needle-free transfer devices, 20-mL empty syringe, preprinted label | 2°C-25°C unopened 2°C-25°C for ≤24 h after reconstitution | Do not inject Do not use for massive or brisk arterial bleeding Hypersensitivity to hamster or snake proteins |

RT, room temperature
for controlling minimal bleeding. Bovine collagen and polysaccharide spheres are considered most effective, and the efficacy of porcine gelatins may be improved when used with topical thrombin.\textsuperscript{30}

*Active* hemostats (Table 5)\textsuperscript{14,49,50} promote clotting by converting fibrinogen to fibrin, with the rate of clot formation proportional to the concentration of both thrombin and fibrinogen.\textsuperscript{51} Topical thrombins are approved for broad surgical use, and standalone thrombin products can be combined with absorbable gelatin sponges. Because topical thrombins are supplied in a number of formulations there are some differences in their requirements for storage and preparation. They are useful for a variety of bleeding scenarios and can be applied locally, with a syringe when bleeding may be difficult to reach, or sprayed over a large area for rapid coverage. Thrombins of all 3 biologic origins are equally effective at controlling local or diffuse bleeding and only slightly more costly than mechanical hemostats.\textsuperscript{30} Topical thrombins will not work unless bleeding is present. Intravascular injection is contraindicated, and thrombin products must not be permitted to enter devices dependent on heparin anticoagulation (eg, blood salvage systems).\textsuperscript{35}

*Flowable* hemostats (Table 6)\textsuperscript{30,35,52,53} combine both active and mechanical hemostat components—and some of the most favorable characteristics of both—to promote clot formation and wound healing. They control bleeding mechanically by obstructing blood flow and, because thrombin is a component, via the rapid conversion of fibrinogen into fibrin. Preparation involves reconstituting thrombin and mixing it with absorbable gelatin particles,\textsuperscript{52,53} a process that may take operating room (OR) staff several minutes but can allow for customized consistency, thorough coverage of a local wound,\textsuperscript{30} and accurate administration (eg, spreading) compared with a liquid thrombin. The FDA also has approved a kit containing porcine gelatin absorbable powder matrix and lyophilized pooled human thrombin, which can be stored at room temperature and prepared quickly. Swelling is a concern with flowable hemostats; excess product should be removed because of this possibility.

*Fibrin sealants* (Table 7)\textsuperscript{54-57} function by increasing the rate of blood clot formation via fibrinogen and thrombin concentrations that are higher at the bleeding site than would normally occur in blood.\textsuperscript{30} These products can be applied locally with a syringe

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### Table 6. Flowable Agents\textsuperscript{30,35,52,53}

<table>
<thead>
<tr>
<th>Clinical Considerations</th>
<th>Risks, Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Porcine gelatin ± thrombin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Surgiflo\textsuperscript{52}</strong></td>
<td>Powder, syringe + flexible applicator tip&lt;br&gt;Store at controlled RT (2°C-25°C)&lt;br&gt;Preparation involves mixing (do not use immediately out of package)&lt;br&gt;Remove excess</td>
</tr>
<tr>
<td><strong>Bovine gelatin + pooled human thrombin</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• FloSeal\textsuperscript{53}</strong></td>
<td>Granular&lt;br&gt;Store at RT&lt;br&gt;3-min reconstitution, mixing\textsuperscript{30}; use mixed product within 2 h&lt;br&gt;Apply as paste, gentle pressure&lt;br&gt;May be reapplied with blunt applicator tip\textsuperscript{35}&lt;br&gt;Remove excess</td>
</tr>
</tbody>
</table>

RT, room temperature

### Table 7. Fibrin Sealants\textsuperscript{54-57}

<table>
<thead>
<tr>
<th>Clinical Considerations</th>
<th>Risks, Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled human plasma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Tisseel\textsuperscript{54}</strong></td>
<td>Freeze-dried: store at 2°C-25°C; do not refrigerate/freeze reconstituted solution&lt;br&gt;Frozen: store at ≤-20°C; thaw 5-105 min (water bath/incubator); do not refrigerate/refreeze after thawing&lt;br&gt;Use within 4 h after reconstitution/thawing&lt;br&gt;Best applied to as dry a field as possible</td>
</tr>
<tr>
<td><strong>Pooled human plasma</strong></td>
<td></td>
</tr>
<tr>
<td><strong>• Evicel\textsuperscript{55}</strong></td>
<td>1 vial each of fibrinogen and thrombin frozen solutions + spray applicator&lt;br&gt;Frozen: store at ≤-18°C for ≤2 y; must be thawed; temperature must be ≤37°C&lt;br&gt;After thawing, use within 24 h if stored at RT, 30 d if stored refrigerated</td>
</tr>
<tr>
<td><strong>Individual human plasma with bovine collagen and bovine thrombin</strong></td>
<td>Single-use 5 mL treatment syringe + sterile delivery components, transfer syringe&lt;br&gt;Combine with an equal volume of patient plasma&lt;br&gt;Store at 2°C-8°C; do not freeze</td>
</tr>
<tr>
<td><strong>Individual human plasma</strong></td>
<td>Single-use unit produces 4 sterile sets of 2 syringes (total volume, 6-16 mL; conditions may affect harvest volume)&lt;br&gt;Store at ≤-18°C for ≤1 y&lt;br&gt;Use within 6 h (at 34°C-37°C)</td>
</tr>
</tbody>
</table>

RT, room temperature
or sprayed over a large area, a feature that makes them beneficial in local and diffuse bleeding. Their use is appropriate in patients with coagulopathy who do not have sufficient fibrinogen to form a clot; however, intact coagulation may be required. Safety concerns include viral or prion disease transmission associated with human plasma derivatives; antibody formation with bovine thrombin; and swelling with bovine collagen. Although a ready-to-use, absorbable patch was FDA-approved for cardiovascular surgery in 2010, a key concern with fibrin sealants generally is the need for surgeons to master skillful application techniques. Another concern is the complexity of coordinating the reconstitution and preparation of these 2-component products by hospital staff.

In some clinical scenarios, non-fibrin sealants (Table 8) or adhesives may be more appropriate. As noted, adhesives are fast-setting agents that join tissues without need for an intact clotting mechanism and polymerize within approximately 30 seconds. For example, albumin plus glutaraldehyde—a polymer with sealant and adhesive properties—is used for vascular sealing of large blood vessels, often in cardiovascular surgeries; it should be used sparingly and applied carefully because of its strong adhesiveness. The surgical team should be familiar with labeling and the clinical particulars associated with each agent, such as coordination of preparation time and application techniques.

### Surgeon Perspectives on Topical Hemostats, Sealants, and Adhesives

The surgeon's approach to hemostasis is influenced by training, judgment, technical skill, and area of expertise and is viewed through a prism of clinical experience. Clinician choice may be influenced heavily by product availability within the hospital. In different surgical scenarios, the type of bleeding encountered will dictate selection of a topical hemostat. For example, in minimal or mild bleeding proximal to an anastomosis (ie, connection of 2 cut ends of a structure to form a continuous channel) after coronary artery bypass graft, surgeons often will select the least expensive type of hemostat (eg, mechanical). Topical thrombin use is appropriate for bleeding from needle holes after suture; cautery in this scenario would compromise the integrity of the anastomosis.

Compression hemostatic agents (eg, oxidized regenerated cellulose and microfibrillar collagen) are the most commonly used adjuncts for anastomotic hemostasis. These agents also are useful in highly vascularized liver surgery, in which diffuse bleeding can be significant and coagulopathy present and the use of compression in combination with application of a mechanical hemostat is a common initial approach. Oxidized regenerated cellulose is bacteriostatic, and there is some evidence—and widespread clinical acceptance—of its effectiveness for suture line bleeding. Oxidized cellulose requires a normal clotting system, and its mechanism appears to be a physical effect rather than via alteration of intrinsic clotting. In contrast, microfibrillar collagen provides some hemostatic effect by initiating of platelet activation and aggregation.

Surgeons may favor specific attributes of products in this class. For example, absence of bulkiness and the degree to which a material will conform to anastomosis may be important at the conclusion of hepatectomy, which is likely to be associated with substantial bleeding in the retroperitoneum "bare area." Similarly, microfibrillar collagen—which is available in many forms—conforms well to bleeding surfaces of the type encountered in a broad spectrum of vascular surgeries.

### Table 8. Non-Fibrin Sealants and Adhesives

<table>
<thead>
<tr>
<th>Clinical Considerations</th>
<th>Risks, Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEG Polymers</strong></td>
<td></td>
</tr>
<tr>
<td>• Coseal</td>
<td>Apply to as dry a field as possible</td>
</tr>
<tr>
<td>• DuraSeal</td>
<td>Avoid dripping to undesired locations</td>
</tr>
<tr>
<td>• ProGel</td>
<td>Swelling</td>
</tr>
<tr>
<td><strong>Cyanoacrylates</strong></td>
<td></td>
</tr>
<tr>
<td>• Dermabond</td>
<td>Use to avoid wound dehiscence associated with deep dermal sutures</td>
</tr>
<tr>
<td>• Omnisil</td>
<td>Keep skin edges exposed for ≥ 20 sec</td>
</tr>
<tr>
<td>• Histoacryl</td>
<td>Avoid dripping to undesired locations</td>
</tr>
<tr>
<td>• Histoacryl Blue</td>
<td>External use only; with deep dermal sutures</td>
</tr>
<tr>
<td>• InDermil</td>
<td></td>
</tr>
<tr>
<td>• SurgiSeal</td>
<td></td>
</tr>
<tr>
<td><strong>Bovine serum albumin + glutaraldehyde</strong></td>
<td></td>
</tr>
<tr>
<td>• Biogluca</td>
<td>Use carefully, sparingly</td>
</tr>
<tr>
<td>• BioGlue</td>
<td>Wall off critical zones of surgical field with sponges/pads to avoid nerve/vessel injury</td>
</tr>
<tr>
<td><strong>Risks, Precautions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Strong adhesiveness</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Experience With Topical Thrombins

Topical thrombins have well-recognized clinical utility. Since the first of these—derived from bovine origins—was introduced in the 1940s, the have continued to increase in prevalence and now are used in more than 1 million patients annually in the United States at a cost of $250 million. The currently available bovine thrombin product was approved in 1995. Compared with earlier versions that contained 20% to 30% thrombin, it is purified chromatographically and processed by ultrafiltration to contain fewer protein contaminants and has been shown to be 96% thrombin. In the past 5 years, thrombins of human and recombinant origins have become available.

In 2007, pooled human plasma–derived thrombin became the second topical thrombin product approved in the United States. It is manufactured using pooled human source and recovered plasma obtained from US-licensed plasmapheresis centers and has a potential risk for viral or prion disease transmission, despite manufacturing steps designed to reduce this risk.

Recombinant thrombin was FDA-approved in 2008. Derived from a genetically modified Chinese hamster ovary cell line, it has a molecular structure very similar to that of human thrombin. Allergic reactions to hamster or snake proteins also used in
manufacturing are potential risks associated with its use\textsuperscript{50}; genetic engineering reduces the risks for antibody formation and eliminates the risk for pathogen transmission.

All 3 thrombin types have similar efficacy,\textsuperscript{70,71} are labeled as aids to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and are indicated for use with an absorbable gelatin sponge.\textsuperscript{14,49,50} Thrombin concentration correlates with reaction rate—the speed at which thrombin causes clot formation\textsuperscript{49,51}; thrombins of all 3 biologic origins are available in concentrations of 1,000 units/mL. As noted, thrombins often are combined with other hemostats or materials and administered in a variety of ways (eg, dripped, sprayed, moistened on gauze, used with gelatin sponge or powder, or combined with gelatin matrix or fibrinogen). Systemic injection is contraindicated for all topical thrombins and can result in extensive clotting, hypotension, and even death.\textsuperscript{14,49,50}

Surgeons should note the labeled contraindications to use for all hemostatic agents; the boxed warning on bovine thrombin states that patients with known antibodies to bovine thrombin preparations should not be re-exposed to these products.\textsuperscript{14} A heightened awareness of previous thrombin exposure may be of particular concern in types of surgery in which subsequent operations may be anticipated (eg, pediatric heart surgery). Concerns about the potential of relatively higher risks for antibody production with the use of bovine thrombin, compared with recombinant thrombin, are noted in guidelines issued in 2011 by the STS Blood Conservation Guideline Task Force.\textsuperscript{16} Conclusions regarding the clinical significance of differences in antibody formation cannot be drawn.

**Efficacy and Effectiveness of Topical Thrombin**

Bovine thrombin—the oldest form of topical thrombin product—has been used effectively in an array of surgical settings. Its efficacy also has been validated in RCTs in which it has been the active comparator in studies evaluating the newer topical thrombins.\textsuperscript{70,71}

Human plasma-derived thrombin was compared with bovine thrombin in a prospective, double-blind, multicenter Phase III RCT of 305 patients.\textsuperscript{71} Doria and colleagues randomized patients undergoing cardiovascular, neurologic, or general surgeries to receive either bovine (n=152) or human (n=153) thrombin administered with a gelatin sponge. Individuals with known antibodies to bovine thrombin were excluded. In both groups, 97.4% of patients achieved the primary end point of hemostasis at 10 minutes. Equivalency in the human and bovine thrombin treatment groups also was demonstrated for hemostasis at 6 minutes (94.8% vs 92.8%, respectively) and 3 minutes (73.2% vs 72.4%, respectively). AEs in both groups were similar and as expected for the procedures, with pruritus being the most common. No patients in the human thrombin group seroconverted for anti-human thrombin or anti-human factor V/Va antibodies, compared with 2.38% (3 of 126) in the bovine thrombin group who developed seroconversion for anti-human thrombin and 7.94% (10 of 126) who developed anti-bovine thrombin antibodies (\(P=0.0015\)). No significant differences were noted in need for transfusions, duration of surgery, or hospital LOS.\textsuperscript{71}

Recombinant thrombin was evaluated for relative efficacy compared with bovine thrombin in a study of 411 patients undergoing spinal surgery, hepatic surgery, peripheral arterial bypass, or placement of an arteriovenous graft.\textsuperscript{70} In this double-blind, multicenter Phase III RCT by Chapman and colleagues, subjects were randomized to receive either recombinant (n=205) or bovine thrombin (n=206), at a concentration of 1,000 U/mL, with an absorbable gelatin sponge; 401 patients completed the study. In both treatment groups, 95% of patients achieved the primary efficacy end point of hemostasis at 10 minutes (bovine thrombin group, 95.1%; recombinant thrombin group, 95.4%), demonstrating comparable efficacy (Figure 2). However, in a post hoc analysis by Weaver and colleagues of patients undergoing peripheral arterial bypass surgery (n=88), hemostasis at 3 minutes was achieved in a significantly greater proportion of subjects receiving recombinant thrombin (35%) than those receiving bovine thrombin (39%).\textsuperscript{72} Incidence of AEs in the Chapman study was similar for the 2 groups; most AEs were as expected for the surgery type and moderate in severity.\textsuperscript{70} Antiproduct antibody development was reported in 1.5% (3 of 198) of the recombinant group, compared with 21.5% (43 of 200) of the bovine group (\(P=0.0001\)) (Figure 3).\textsuperscript{70} There was no causal association between antibody development and any AEs in either treatment group. Pooled safety data from 8 clinical trials also have shown that recombinant thrombin is well tolerated with a low rate of antibody formation.\textsuperscript{74}

The clinical effects of immunogenic response to topical bovine thrombin also have been evaluated. An open-label, prospective, observational case cohort study by Paterson et al assessed the effect on clinical hemostasis of human antibodies to bovine thrombin or factor V/Va in response to topical bovine thrombin in patients with and without preexisting anti-bovine antibodies.\textsuperscript{74} The study enrolled 550 patients who underwent surgery with bovine thrombin administered at surgeon’s discretion. Patients were assigned to 1 of 4 cohorts based on presurgery presence or absence of antibody to bovine thrombin (\(aBT\)), and use or nonuse of bovine thrombin during study surgery; 481 patients assigned to cohorts completed the study. The hypothesis was that patients with presurgery \(aBT\) administered the bovine thrombin during surgery would experience postsurgical changes from baseline aPTT that were not clinically different (ie, were noninferior) to those in patients without presurgery \(aBT\) and who did not receive bovine thrombin in surgery. Based on adjusted mean change in aPTT values at 48 hours postsurgery, the study failed to establish noninferiority between primary cohorts (noninferiority was defined as 15% shift from baseline; reference value, 30 seconds).

In secondary end point analyses, the number of bovine thrombin-treated patients with human anti-bovine factor V/Va antibodies (\(aBV/Va\)) increased at weeks 4 and 8 postsurgery compared with 48 hours. At 4 weeks postsurgery, 70% of evaluable patients (n=50) in the cohort of patients with (+)presurgery \(aBT\)/(+)bovine thrombin exposure had cross-reacting antibodies to factor V, compared with 52% (n=39) at 48 hours; in the cohort with (+)presurgery \(aBT\)/(-)bovine thrombin exposure during surgery, 12% of patients (n=14) had cross-reacting antibodies to factor V at week 4, compared with 8% (n=10) at 48 hours. However, no immunologic markers at 48 hours or weeks 4 or 8 were related to changes in coagulation parameters. The study’s major limitation was its observational design, which precluded drawing conclusions about causality.

**Recognition and Management of IMC**

Distinctions are recognized between technical causes of surgical bleeding (eg, inadequate repair of vessels, intraoperative injury, or damage to organs) and coagulopathy, or disorders of hemostasis.\textsuperscript{15,75} These can result from therapeutic coagulation, acidosis, enzymatic
dissolution of fibrin related to CPB, heparin-induced thrombocytope尼亚，liver dysfunction, disseminated intravascular coagulation, inaction or dissolution of fibrinogen in the blood (fibrinogenolysis), consumptive loss of coagulation factors, hypothermia, or other mechanical and metabolic derangements. Postsurgical coagulopathy, consumptive loss of coagulation factors, hypothermia, or other inaction or dissolution of fibrinogen in the blood (fibrinogenolysis). 

IMC can further complicate clinical recognition of IMC; inhibitors typically develop 7 to 10 days after a primary exposure during surgery, but specific factor V antibody assays generally are not. Although rare, acquired factor V deficiency can induce coagulation defects and severe bleeding complications.

Although its precise incidence is not known, bovine thrombin-associated IMC has been recognized for more than 20 years as a distinct type of acquired coagulopathy, and identified by the Joint Commission as an iatrogenic and preventable complication that poses a threat to patient safety and warrants increased attention. Its recognition poses clinical challenges, partly because clinician awareness of IMC is believed to be low—particularly among surgeons—and its incidence may be underreported. One reason for this is the lack of a predictable pattern of antibody response or coagulopathy development. A consensus panel's review of 64 case reports in which exposure to bovine thrombin was known or presumed found near-equal representation of bleeding and nonbleeding presentations. There is incomplete evidence to guide the management of IMC, particularly when it is accompanied by clinically significant bleeding. Platelet therapy may be reasonable because of the store of factor V on platelet surfaces, although treatment approaches are speculative, and supportive care is patient-specific. Corticosteroids, IV immunoglobulin therapies, and plasma products enter hospitals via central surgical supply rather than being purchased through the pharmacy department, however, such documentation often is not available. Coagulation factor inhibitors should be suspected in patients with unexplained postoperative bleeding in the presence of prolonged PT and aPTT; if a mixing study (1:1 mix of patient plasma with normal pooled plasma) fails to correct, an inhibitor may be considered the presumptive cause, and a hematology consult should be requested. Specific quantitative assays of factor V and factor V inhibitor may be conducted (factor V assays are available readily in most laboratories, but specific factor V antibody assays generally are not).

The challenges of managing an acquired factor inhibitor are formidable. One reason for this is the lack of a predictable pattern of antibody response or coagulopathy development. A consensus panel's review of 64 case reports in which exposure to bovine thrombin was known or presumed found near-equal representation of bleeding and nonbleeding presentations. There is incomplete evidence to guide the management of IMC, particularly when it is accompanied by clinically significant bleeding. Platelet therapy may be reasonable because of the store of factor V on platelet surfaces, although treatment approaches are speculative, and supportive care is patient-specific. Corticosteroids, IV immunoglobulin therapies, and plasma products enter hospitals via central surgical supply rather than being purchased through the pharmacy department, however, such documentation often is not available. Coagulation factor inhibitors should be suspected in patients with unexplained postoperative bleeding in the presence of prolonged PT and aPTT; if a mixing study (1:1 mix of patient plasma with normal pooled plasma) fails to correct, an inhibitor may be considered the presumptive cause, and a hematology consult should be requested. Specific quantitative assays of factor V and factor V inhibitor may be conducted (factor V assays are available readily in most laboratories, but specific factor V antibody assays generally are not).

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Roles for the Hospital Pharmacist and Nurse In Optimizing Topical Hemostasis

Together with medical staff, the hospital pharmacist’s role shares responsibility for formulary selections and the development of policies that minimize drug errors and assure
medication safety.92,94 Surgical hemostasis is an area that presents many opportunities for multidisciplinary collaboration by pharmacists, surgeons, anesthesiologists, hematologists, nurses, and others—particularly in the setting of the Pharmacy & Therapeutics (P&T) Committee.

The primary responsibility of the P&T committee is formulary management via the clinical judgment of a range of professionals in the diagnosis, prevention, or treatment of disease and promotion of health.94 The formulary itself represents the ongoing selection of the most medically appropriate and cost-effective products and therapies to serve the health interests of a given patient population.93,95 This process is informed primarily by published reports (eg, RCTs, reviews, drug monographs, addenda), which provide new evidence concerning drug efficacy, stability, tolerability, methods of administration, cost, and pharmacoeconomics and may warrant reevaluation of agents used, dosage strengths, or formulations stocked by a hospital or health system.96 Information for appraisal in P&T also comes from practice guidelines, labeling revisions, AE updates, FDA announcements, expert opinion, and internal data. These sources may be particularly important in therapeutic areas for which there is a limited evidence base to guide clinical decision making. For example, a 2010 Joint Commission newsletter reported that bovine thrombin-associated IMC may occur days to weeks after surgery and should be considered in the differential diagnosis in cases of unexplained postoperative bleeding or unexplained PT, aPTT, or thrombin time in the absence of bleeding.81

Although the perception among medical staff may be that the P&T committee is an entity best left alone to do its work, the literature shows that safety is best evaluated by an interdisciplinary group of health care providers who may uncover potential hazards of use before an agent is introduced to the formulary.91 In fact, adherence to department “silo” mentalities or budgets may suggest an unwillingness to take into account available evidence reflecting improved patient outcomes or decreased total costs.24 A physician who deals with acute or surgical bleeding can contribute to formulary decision making by sharing clinical, safety, and availability concerns about drug classes or specific agents, especially if scientific evidence or direct comparisons of various agents are lacking.

All P&T members should be involved in disseminating information on the decisions made and the rationales thereof. For pharmacists, a primary responsibility is the effective communication of actions related to the medication use evaluation process to ensure that policy is integrated into therapeutic decision making.94 Specifically, in-service education, grand rounds, interaction with other clinicians at the time of dispensing, staff meetings, email, newsletters, mailings, prescriber detailing, and pharmacy or institutional Web sites offer opportunities for targeted communication.94 These and other methods can be used by pharmacists to help establish and support a culture of medication safety.

In the setting of surgical hemostasis and acute bleeding, pharmacists may participate in a range of efforts to reduce transfusion rates or enhance the safety of topical hemostat use. One example pertains to minimizing the risk for accidental intravascular administration, a danger addressed in warnings from both the FDA and the Institute for Safe Medication Practices.96,97 Despite cautionary labeling on all topical thrombin products, instances of inadvertent injection are documented, and one such event was fatal.97 Similarities in packaging for topical thrombin and parenteral products (ie, vial and syringe) may contribute to the potential for misadministration. This suggests opportunities for pharmacist involvement in communicating with clinicians who make therapeutic decisions at the point of care; for example, auxiliary “Do Not Inject” labeling of syringes used in thrombin reconstitution may help reduce the risk for misadministration.

Nurses are on the front lines of safety in the OR and perioperative setting as well and should be involved in safe-use initiatives, such as safety checklists (Figure 4).97 Nurses are responsible for communicating the presence of topical thrombin in the sterile field and are expected to try to delay introducing it until after all parenteral products have been administered. Manufacturers of topical hemostats recognize this and include OR nurses as a key target audience for instructional information. Similarly, some fibrin sealant product labeling specifically addresses scrub and circulating nurses, providing detailed information on safe transfer of the fibrinogen component to the sterile field.

Pharmacoeconomic review is another important element in the review of all products. Generally done by pharmacists working with other health care professionals and the purchasing department, this evaluation considers acquisition price as well as indirect costs related to storage, preparation, management of complications associated with use and effect on patient care. Among average wholesale prices for topical hemostats, topical thrombins generally are less costly than flowables and somewhat more costly than mechanical hemostats, with fibrin sealants generally the most

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**An IMC Case Report**

The significant consumption of blood and blood products, LOS, and use of other resources are incremental cost drivers in the management of IMC, as illustrated in a recent case report of a 76-year-old woman who developed severe hemorrhagic complications after surgical exposure to bovine thrombin.93 Initially she was diagnosed with disseminated intravascular coagulation but continued to experience episodic bleeding. Eventually, mixing studies and clotting factor assays revealed significantly reduced factor V activity (<5% of normal) and an ongoing IMC, and inhibitor titer assay confirmed the presence of a factor V inhibitor. The patient’s critical care hospitalization lasted 64 days and required 282 units of blood products and 2 reoperations in addition to other resources (Table 9)93 for a total cost of $444,996.

### Table 9. Costs Associated With IMC Case

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cost/Unit, $</th>
<th>Units</th>
<th>Total Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS (no ventilator)</td>
<td>4,022/d</td>
<td>64</td>
<td>257,408</td>
</tr>
<tr>
<td>Blood products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed RBCs</td>
<td>1,459</td>
<td>78</td>
<td>113,802</td>
</tr>
<tr>
<td>FFP</td>
<td>72</td>
<td>129</td>
<td>9,288</td>
</tr>
<tr>
<td>Platelets</td>
<td>656</td>
<td>62</td>
<td>40,672</td>
</tr>
<tr>
<td>IVIG</td>
<td>181</td>
<td>132</td>
<td>23,826</td>
</tr>
<tr>
<td><strong>Total estimated cost</strong></td>
<td></td>
<td></td>
<td><strong>444,996</strong></td>
</tr>
</tbody>
</table>

FFP, fresh frozen plasma; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LOS, length of stay; RBC, red blood cell.
expensive topical hemostats. Pricing for thrombins of all 3 biologic origins is competitive, with human thrombin products incrementally—although not excessively—more costly than bovine thrombin; acquisition costs vary by institution based on contract pricing, purchasing group criteria, and volume usage.

Waste reduction is a key consideration in the pharmacoconomics review process. In a 9-month university hospital study that evaluated a switch from the formulary thrombin (bovine-derived, 20,000-IU vials with spray applicators) to recombinant thrombin (5,000-IU vials with or without a spray kit), the switch yielded a savings of $92,396 (38%), an apparent consequence of reducing product waste and mixing smaller quantities of thrombin for use with a sponge or sprayer.98

Making Sense of the Science: Understanding Clinical Research

As noted, formulary decisions are based in part on a critical evaluation of the literature. With the dynamic flow of research and increasing demands on health care providers, many clinicians report that they cannot always read the medical literature critically.99 Thus, a review of concepts is appropriate.

Studies must be evaluated and understood in the context of the research hierarchy. Often, this is represented as a pyramid with systematic reviews and meta-analyses at the top, followed by evidence guidelines and summaries; RCTs, case cohorts and nonrandomized controlled studies; clinical research critiques; literature reviews; case reports, case series, and practice guidelines; and clinical reference texts. Because meta-analyses and systematic review are only as strong as the quality of research being reviewed, it is important to understand the additional elements of study design and appraise commonly used measures.

Most clinical research can be categorized broadly as experimental (randomized or nonrandomized) or observational (analytical or descriptive). The experimental RCT represents the gold standard of investigations designed to evaluate an intervention because the assignment of a subject to an exposure is done purely by chance rather than by the investigator.99 A good RCT also minimizes selection and confounding biases in the determining outcomes.99 One limitation is the potential for an RCT to lack external validity—the extent to which results can be generalized to the broader community as opposed to a more homogenous trial population.

Observational studies track subjects forward in time from exposure or nonexposure to outcome (or involve control subjects who are identified retrospectively). Finally, case–control studies trace backward from outcome to exposure (eg, epidemiologic studies to track outbreaks of food-borne illness), and descriptive studies (eg, case series reports) do not have a comparison group; thus investigators cannot examine associations.

Insightful review of design and methodology, including dropout rate, patient demographics, interventions, and power, can shed light on the complexities of any study and determine the applicability of that work to the practice changes. In meta-analyses, attention to study selection is key. The authors of the 2007 STS/SCA practice guideline for blood transfusion and conservation used a systemic, comprehensive literature search to make their recommendations.100 In so doing, they searched MEDLINE, EMBASE, CINAHL, and the Cochrane Collaboration. Had they used only used one database, MEDLINE, for example, their results would have been skewed; MEDLINE only contains approximately one-third of the world’s medical literature, with poor representation in such subspecialties as cardiothoracic surgery.

It is also important to understand the various parameters that are to report study results. Commonly used are relative risk, the probability of the event occurring in the exposed group versus a non-exposed group, and absolute risk reduction, the amount by which therapy reduces the risk for an undesirable outcome. These and other measures of association express results of dichotomous

Have pharmacy prepare label, dispense drug, including doses for operating room ✓

Never leave vial/syringe at patient’s bedside where it could be confused with parenteral product ✓

Apply auxiliary warning labels to syringes containing thrombin: “For topical use only—do not inject” ✓

Communicate presence of product in sterile field, delay doing so until all parenteral products have been administered ✓

Differentiate parenteral, topical products by using absorbable gelatin sponge or dry form when possible ✓

Consider using spray kits to differentiate thrombin from parenteral products; never leave syringe unlabeled before applying spray mechanism ✓

Figure 4. Thrombin safety checklist.97
outcomes (eg, sick vs healthy). Studies also often use P-value and/or confidence interval to report statistical data. Confidence interval may be particularly useful because it indicates strength, direction, and a plausible range of effect, as well as the likelihood of chance occurrence. Finally, another useful tool is the number needed to treat (NNT), defined as the number of patients who must be treated to prevent one additional undesirable outcome (Figure 5). The result is useful in determining how much of an effect a study outcome will have on the care of a patient population and how many patients might benefit versus the number exposed to the treatment.

Clinical Application of RCT Data

Both the Chapman and Doria investigations are of good quality and highlight the application of some of the principles discussed above. One notable aspect of the Chapman study is its group sequential design with a flexible sample size; investigators sought to enroll 400 to 600 patients to provide an adequate safety evaluation and expose a minimum of approximately 200 patients to recombinant thrombin. This design allowed as many as 3 interim analyses (2 were conducted), and the maximum number of patients was computed to maintain 99.5% power to declare comparable efficacy when the 2 treatments were equivalent. At the second interim analysis, available data were deemed sufficient, and the independent data monitoring committee recommended that the study continue as planned until 400 patients with evaluable efficacy data were enrolled. On the primary end point of hemostasis at 10 minutes, the study showed no difference between the 2 thrombin products. A limitation of the work is that no placebo group was included.

In the Doria RCT, a sample size of 278 was selected based on the assumption that the success rate in the control group would be 77%. This allowed investigators to ascertain equivalence with 95% confidence and 90% power; the sample size was increased to 304 to allow for potential dropouts. Efficacy and safety analyses were performed using an intent-to-treat population. Hemostasis equivalence was demonstrated in both treatment groups. Limitations included no placebo-control group, potential intersurgeon variability in application technique and hemostasis assessment, and antibody assessment not evaluable for all patients.

In both the Chapman and Doria studies, the surrogate marker of hemostasis at 10 minutes was the primary efficacy end point—a very practical measurement of the desired clinical effect, absence of bleeding from the surgical site. There was no difference in the primary outcome, so a NNT could not be calculated.

**Conclusion**

Excess bleeding is associated with a continuum of clinical and economic outcomes. A multimodal approach to perioperative hemostasis requires familiarity with hemostat characteristics and limitations. Topical hemostats are integral elements of the surgeon’s tool kit, and all members of the multidisciplinary care team must be knowledgeable about these important adjuncts to hemostasis. Among the most widely used topical hemostats are thrombins, which are available for use as standalone products or in conjunction with other agents. Topical thrombins have demonstrated similar efficacy in a limited number of studies; however, the risks for viral or disease transmission or development of cross-reacting antibodies against endogenous coagulation factors may be higher with human- and bovine plasma-derived products, respectively. Cross-reacting antibodies have been implicated, although rarely, with IMC and carry the potential for clinically severe bleeding events. As such, clinicians would be prudent to remain vigilant about the issues with use and documentation of thrombin products in the surgical setting, whether as standalone or combination products, as well as the diagnosis and management of IMC.

Surgeons, pharmacists, and perioperative nurses share in the responsibilities—in the OR and beyond—of achieving intraoperative hemostasis through the optimal selection and use of available hemostatic agents.

| Is this a meaningful parameter? | NO |
| Can this end point be phrased as a “yes/no” question? | NO |
| Is there a statistical difference between the 2 groups? | NO |

**Calculation**

\[
1 / (p_B - p_A)
\]

• \(p_A\), probability of desired outcome in intervention group
• \(p_B\), probability of desired outcome in control group

**Interpretation**

• Ideal NNT = 1, indicating that all subjects improve with treatment and none improves with control
• Increasing NNT = less effective treatment

**Figure 5. Number needed to treat.**

\(NNT\), number needed to treat

---

**Cannot be calculated**
References

57. CryoSeal (fibrin sealant) [brochure]. Rancho Cordova, California: Thermogenesis Corp; 2006.
60. DuraSeal Dura Sealant System [package insert]. Waltham, MA: Confluent Surgical, Inc; (no year given).
61. ProGel pleural air leak sealant [instructions for use]. Irvine, CA: Neomend, Inc; (no year given).