The estimated time to complete this activity is 60 minutes. This activity is provided free of charge and is available from March 15, 2013 through May 15, 2014.

System Requirements

**Web Browser:** Microsoft Internet Explorer, Mozilla Firefox, Apple Safari or Google Chrome.

Note: Please disable any "pop-up blocker" features.

**Software:** Adobe Acrobat Reader version 7 or above to view PDF files (If you do not have Acrobat Reader, you can download it for free from get.adobe.com/reader).

**Connection Speed:** Cable, DSL, or better of at least 300 kbps.

Target Audience

This activity was planned to meet the needs of health-system pharmacists, especially those providing patient care in the critical care or surgical intensive care setting.

Learning Objectives

After participating in this knowledge-based activity, participants should be able to:

1. Discuss the risk for and potential clinical and economic consequences from perioperative bleeding in surgical patients.
2. Explain the physiology of hemostasis, including activation of platelets and clotting factors, the cell-based model for coagulation, and fibrin clot formation, in response to injury (surgery).
3. Identify a preventive measure, surgical technique, and systemic intervention to reduce the risk for perioperative bleeding, the need for blood transfusion, or both.
4. Name three characteristics of the ideal local hemostatic agent; compare and contrast the mechanism of action, efficacy, safety, ease of use, and cost of various local hemostatic products; and identify a patient-specific consideration in selecting a product.
5. Describe pharmacoeconomic considerations in making formulary decisions about local hemostatic products.
Executive Summary

Perioperative bleeding is a common cause of morbidity and mortality in surgical patients. A variety of strategies, including preventive measures, surgical techniques, and systemic and local interventions, may be used to reduce the risk for anemia and need for blood transfusion due to perioperative bleeding. Adverse effects associated with systemic interventions may be avoided by the use of local hemostatic agents, including mechanical agents, active agents, flowable agents, and fibrin sealants. The mechanism of action, ease of use, efficacy, safety, and cost differ among these local products. These differences and clinician preferences should be taken into consideration in making formulary decisions. Indirect costs should be considered as well as acquisition costs, and institutional guidelines should be developed to optimize the use of local hemostatic agents.

Reviewers and Disclosures

The assistance of the following reviewers of this educational activity is gratefully acknowledged. In accordance with the Accreditation Council for Continuing Medical Education’s Standards for Commercial Support and the Accreditation Council for Pharmacy Education’s Guidelines for Standards for Commercial Support, ASHP Advantage requires that all individuals involved in the development of activity content disclose their relevant financial relationships and that conflicts of interest be identified and resolved prior to delivery of the activity.

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Ms. Dombrowski declares that she has no relationships pertinent to this activity.

ASHP staff has no relevant financial relationships to disclose.
Introduction

Roughly 30% of hospitalized patients undergoing surgery experience perioperative bleeding-related complications, although the incidence varies with the type of surgery and patient-specific risk factors (Table 1). Perioperative bleeding is associated with substantial morbidity and mortality, and it increases the hospital length of stay and costs. The possible clinical consequences of perioperative bleeding include anemia, tissue hypoxia, hemodynamic instability, hypovolemia, and coagulopathy (depletion of clotting factors).

Blood transfusions may be used to manage anemia associated with perioperative bleeding, but serious risks are associated with transfusions, including acute and delayed transfusion reactions, transfusion-related acute lung injury, incorrect blood component transfused, and transfusion-transmitted infection. Substantial costs are associated with the use of transfusions and these adverse events. Bleeding complications or the need for transfusion in surgical patients results in prolongation of the hospital length of stay by 6 days on average and the intensive care unit length of stay by 2.8 days on average at a substantial incremental cost.

Physiology of Hemostasis

Hemostasis after injury to a vessel or tissue (e.g., surgical incision, trauma) is the result of a complex, coordinated process involving vasoconstriction, platelet activation, formation of a soft platelet plug, and fibrin clot formation. Exposure to collagen in the vascular wall activates platelets, increasing their adherence and resulting in aggregation and formation of a soft platelet plug at the site of injury. Thrombin (clotting factor IIa) plays a central role in hemostasis because it catalyzes the conversion of fibrinogen to fibrin. Cross linking of fibrin creates a mesh that strengthens the platelet plug, resulting in formation of a fibrin clot.

A cell-based model for coagulation involving cellular and humoral elements has been put forth to supersede the traditional view of the coagulation cascade with independent intrinsic and extrinsic pathways and a final common pathway because of limitations in the traditional cascade model. The cell-based model is more complex than the traditional model, with extrinsic and intrinsic pathways that are linked and interdependent.
In the priming phase, a small amount of thrombin binds to platelets at the site of injury, enhances platelet activation, and causes the release of partially-activated FV followed by full activation to FVa. In the propagation phase, large amounts of thrombin are produced as a result of binding of FXa to FVa on the platelet surface, leading to formation of a stable fibrin clot.

**Preventive Measures**

A variety of interventions may be used to reduce modifiable risk factors for perioperative bleeding (e.g., discontinuing or temporarily interrupting anticoagulant or antiplatelet therapy), the need for transfusions (e.g., preoperative autologous blood donation), or both. Preoperative administration of erythropoiesis-stimulating agents (e.g., epoetin alfa, darbepoetin alfa) with iron may be used to increase red blood cell mass in selected patients with preoperative anemia or a high risk for postoperative anemia, patients who underwent preoperative autologous blood donation, and patients who refuse transfusion for religious reasons (e.g., Jehovah’s witnesses). Other blood conservation techniques, particularly the use of alternatives to laboratory blood sampling (e.g., oximetry instead of phlebotomy to measure arterial blood gases) or other strategies to minimize the amount of blood drawn for testing, may reduce the risk for anemia and the need for transfusions.

**Surgical Techniques**

Various mechanical and thermal techniques have been used to maintain hemostasis during surgery. Applying direct pressure or using compression at the bleeding site, a mechanical intervention that usually is the preferred option, may not be feasible when bleeding is diffuse or associated with medications. Other mechanical interventions include sutures, staples, and ligating clips. These interventions are useful for bleeding at a specific site, but may be of limited use in patients without localized bleeding.

Electrocautery, lasers, harmonic frequency devices (e.g., scalpel, shears), argon beam coagulation, and radiofrequency technology are thermal techniques that produce coagulation by generating heat. Some of these technologies are relatively expensive.

**Systemic Interventions**

Systemic interventions to manage perioperative bleeding include transfusion of selected blood products and the use of systemic hemostatic agents. Administration of blood products (e.g., fresh frozen plasma, prothrombin complex concentrates, platelets) can be helpful for replenishment in patients with deficiencies of clotting factors or platelets. However, administration of blood products is accompanied by the infectious and non-infectious risks associated with blood transfusion. In trauma patients, transfusion of red blood cells stored for 28 days or longer is associated with an increased risk for deep vein thrombosis and mortality compared with red blood cells stored for shorter periods.

Recombinant factor VIIa, a product approved by the Food and Drug Administration (FDA) for prevention and treatment of bleeding in patients with hemophilia A or B, has been used off-label to manage uncontrolled, life-threatening bleeding in patients without hemophilia. A wide range of dosages have been used, with equivocal efficacy results in these non-hemophilic patients. Thromboembolic adverse events are a safety concern with use of the product.

The lysine analogs epsilon aminocaproic acid and tranexamic acid have antifibrinolytic activity that reduces blood loss during surgery and the need for blood transfusion. They are administered intravenously. Tranexamic acid has a greater effect than epsilon aminocaproic acid. Tranexamic acid should be considered for patients with serious bleeding due to trauma because in a large, randomized, placebo-controlled study of such patients, the drug significantly reduced the risk of death from bleeding and all-cause mortality.
Unwanted clotting is a potential complication of antifibrinolytic agents. Aprotinin is an antifibrinolytic agent that was used to manage perioperative bleeding in the past, but it was removed from the market in 2007 because an increased risk for cardiovascular complications and death was associated with its use.

Other systemic options for managing perioperative bleeding in selected patients include vitamin K and the vasopressin analog desmopressin. Desmopressin is used to prevent or treat bleeding in patients with von Willebrand disease, a congenital bleeding disorder associated with von Willebrand factor deficiency. The drug is not effective for minimizing the need for perioperative blood transfusion in patients without this congenital bleeding disorder.

**Local Interventions**

The adverse effects associated with systemic interventions may be avoided through the use of local interventions, which allow flexibility in use of only as much product as is needed based on the amount of bleeding. However, local interventions are not necessarily less expensive or easier to prepare, use, or store than systemic interventions. Local interventions include hemostatic agents, sealants, and adhesives. Hemostatic agents cause blood to clot, sealants form a barrier to prevent blood and other fluids from leaking from tissues, and adhesives hold tissues together. All three types of local interventions have hemostatic effects and can be used to prevent or stop perioperative bleeding.

**Hemostatic Agents**

Properties of the ideal local hemostatic agent include rapid efficacy in controlling bleeding, acceptable adverse event profile, availability in multiple forms for versatility, ease of use (i.e., handling, preparation, application), stability at room temperature, and affordability. None of the currently available local hemostatic agents is ideal. The currently available local hemostatic agents may be classified as mechanical agents, active agents, flowable agents, or fibrin sealants.

**MECHANICAL AGENTS**

Mechanical hemostatic agents provide a physical surface to block blood flow and expedite clotting. These absorbable agents are available in various forms, including sponges, sheets, strips, and powders that are ready to use, with no special storage or preparation requirements. Products available as sheets or strips may be cut to size.

Mechanical hemostats are used in surgical procedures when conventional methods of hemostasis (e.g., pressure, ligature) are ineffective or impractical. These agents should not be placed in or injected into blood vessels because of the risk for embolization. Mechanical hemostatic agents are useful only for minimal bleeding. Their ease of use, low cost, and relative safety are advantages over other local hemostatic agents. Swelling and expansion of mechanical hemostatic agents is a concern because it can lead to compression of surrounding tissues, including nerves. Therefore, most products should not be used for surgeries in closed cavities or ophthalmologic or urologic surgeries. The amount of these products used should be minimized. Although mechanical hemostatic products are absorbable, most products should be removed to the extent possible once bleeding is controlled before wound closure.

Mechanical hemostats include porcine gelatin, bovine collagen, oxidized regenerated cellulose, and polysaccharide spheres. Although these agents all provide passive hemostasis, they differ somewhat in their mechanism of action, efficacy, and safety. A risk for allergic or immune reaction is associated with products of animal origin (i.e., porcine gelatin and bovine collagen). Products provided as sponges in theory may cause foreign body reactions.

Porcine gelatin foam is made from pig skin and processed into a sponge or powder form. Porcine gelatin sponges have been available since 1945. Porcine gelatin powders become a paste with the consistency of putty when mixed with sterile saline. The paste is useful for application to irregular surfaces.

Bovine collagen is obtained from the skin or Achilles tendon of cows. It is available as sheets, sponges, pads, flour, and fibrillar or microfibrillar material (i.e., filaments or fiber). Some flours are provided in syringes or applicators. The microfibrillar form was introduced in the early 1970s and is characterized by high tensile strength. Bovine collagen promotes platelet aggregation, degranulation, clotting factor...
### Table 2
Local Hemostatic Agents

<table>
<thead>
<tr>
<th>CLASS/TYPE OF AGENT</th>
<th>PRODUCT NAME (FORM)</th>
<th>MECHANISM OF ACTION</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porcine gelatin</td>
<td>Gelfoam (sponge and powder)</td>
<td>Form matrix for clot formation, serve as barrier to blood flow</td>
<td>May be more effective if used with local thrombins than when used alone</td>
<td>Risk for allergic/immune reaction to porcine proteins; Sponges may cause foreign body reactions</td>
</tr>
<tr>
<td>Bovine collagen</td>
<td>Avitene (sheets, flour, and foam sponges)</td>
<td>Form matrix for clot formation; serve as barrier to blood flow; promote platelet aggregation, degranulation, clotting factor release, and clot formation</td>
<td>More effective than porcine gelatin and oxidized regenerated cellulose</td>
<td>Risk for allergic/immune reaction to bovine proteins; Sponges may cause foreign body reactions</td>
</tr>
<tr>
<td>Oxidized regenerated cellulose</td>
<td>Surgicel (knitted fabric strips)</td>
<td>Form matrix for clot formation, serve as barrier to blood flow, risk of infection but not as well absorbed as other mechanical hemostats</td>
<td>Acid bactericidal environment may reduce risk of infection but inactivates thrombin (not useful with local thrombins)</td>
<td>May cause foreign body reactions</td>
</tr>
<tr>
<td>Polysaccharide spheres</td>
<td>Arista AH (powder in bellows applicator)</td>
<td>Serve as barrier to blood flow, dehydrate and concentrate blood, and promote platelet and clotting factor function</td>
<td>More effective than porcine gelatin and oxidized regenerated cellulose</td>
<td>Caution in use of large amount in patients with diabetes due to glucose load</td>
</tr>
</tbody>
</table>

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<tr>
<th>CLASS/TYPE OF AGENT</th>
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<th>ADVANTAGES</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>ACTIVE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine thrombin</td>
<td>Thrombin-JMI (sterile powder for use dry or constitution and use as solution or spray)</td>
<td>Active Convert fibrinogen to fibrin</td>
<td>Effective for both localized and diffuse bleeding Relatively easy to prepare and use</td>
<td>Risk for immune-mediated coagulopathy</td>
</tr>
<tr>
<td>Pooled human plasma-derived thrombin</td>
<td>Evithrom (lyophilized powder for constitution and use as solution)</td>
<td></td>
<td>Theoretical risk for transmission of viruses and prions Slightly more expensive than bovine thrombin Not available for use as a spray</td>
<td></td>
</tr>
<tr>
<td>Recombinant human thrombin</td>
<td>Recothrom (lyophilized powder for constitution and use as solution or spray)</td>
<td></td>
<td>Safe for patients with antibodies to bovine thrombin or previous exposure to recombinant human thrombin</td>
<td>Risk for allergic/immune reaction to hamster or snake proteins Slightly more expensive than bovine thrombin</td>
</tr>
</tbody>
</table>
### Table 2 (Continued)

<table>
<thead>
<tr>
<th>CLASS/TYPE OF AGENT</th>
<th>PRODUCT NAME (FORM)</th>
<th>MECHANISM OF ACTION</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLOWABLE</strong></td>
<td></td>
<td>Passive and active</td>
<td></td>
<td>High cost</td>
</tr>
<tr>
<td>Serve as barrier to blood flow and convert fibrinogen to fibrin</td>
<td>Effective for localized bleeding</td>
<td>Conform to irregular surfaces</td>
<td>May be more effective than porcine gelatin sponges plus thrombin</td>
<td>Relatively easy to prepare</td>
</tr>
</tbody>
</table>

- **Bovine gelatin particles plus pooled human thrombin**
  - Floseal (lyophilized thrombin powder for constitution, then addition to gelatin particles to form paste-like mixture)
  - Risk for swelling and compression of surrounding tissues from gelatin
  - Risk for allergic/immune reaction to bovine proteins
  - Theoretical risk for transmission of viruses and prions

- **Porcine gelatin particles with pooled human thrombin or alone for use in combination with bovine, pooled human, or recombinant human thrombin**
  - Surgiflo (gelatin particles provided alone for use with bovine, pooled human, or recombinant human thrombin from separate source and kit with gelatin particles and lyophilized pooled human thrombin powder for constitution and mixing to form paste-like mixture)
  - Risk for swelling and compression of surrounding tissues from gelatin
  - Risk for allergic/immune reaction to porcine proteins
  - Safety concerns associated with thrombin component

<table>
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<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIBRIN SEALANT</strong></td>
<td></td>
<td>Active</td>
<td></td>
<td>High cost</td>
</tr>
</tbody>
</table>

- **Pooled human plasma containing fibrinogen and thrombin**
  - Evicel (frozen solution)
  - Tisseel (frozen solution, lyophilized powder)
  - Complex to prepare and use
  - Theoretical risk for transmission of viruses and prions
  - Risk for anaphylactic reaction to aprotinin in Tisseel

- **Bovine collagen and bovine thrombin with autologous human plasma**
  - Vitagel (suspension)
  - Passive and active
  - May be more effective for providing hemostasis than bovine collagen alone
  - Avoids risk for transmission of viruses and prions from donor plasma used in other fibrin sealants
  - Complex to prepare and use
  - Risk for allergic/immune reaction to bovine proteins
  - Risk for immune-mediated coagulopathy

- **Pooled human plasma fibrinogen and thrombin integrated into equine collagen patch**
  - Tachosil (patches)
  - Passive and active
  - Ease of use without preparation
  - Facilitates the application of pressure
  - Theoretical risk for transmission of viruses and prions
  - Risk for allergic/immune reaction to equine proteins
  - Particularly high cost

- **Pooled human plasma fibrinogen and thrombin integrated into oxidized regenerated cellulose patch**
  - Evarrest (patches)
  - Passive and active
  - Ease of use without preparation
  - Facilitates the application of pressure
  - Theoretical risk for transmission of viruses and prions
  - Risk for hypersensitivity reaction
release, and clot formation in addition to serving as a barrier to blood flow.\textsuperscript{31,32} Bovine collagen products may be the most effective among the mechanical hemostatic products.\textsuperscript{32,57}

Oxidized regenerated cellulose is a cotton plant-derived product that was introduced in 1960.\textsuperscript{15,56} It produces an acid bactericidal environment that may reduce the risk of infection, although this environment inactivates thrombin and may increase inflammation and delay wound healing.\textsuperscript{15,30}

Polysaccharide spheres are a plant-derived starch. The mechanism of action of these products in providing surgical hemostasis involves dehydrating and concentrating blood and promoting platelet and clotting factor function.\textsuperscript{32} These products are supplied as a powder in a bellows applicator that is ready to use.\textsuperscript{42,43} Polysaccharide spheres may be more effective for providing surgical hemostasis than porcine gelatin and oxidized regenerated cellulose.\textsuperscript{30,58} Polysaccharide spheres should be used in limited amounts in patients with diabetes mellitus because of the glucose content.\textsuperscript{32}

**ACTIVE AGENTS**

Bovine thrombin, pooled human plasma-derived thrombin, and recombinant human thrombin are considered active agents because of their effect on the final common pathway of coagulation. They are used as an aid to hemostasis when oozing of blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard techniques (e.g., sutures) is ineffective or impractical.\textsuperscript{44–46} Thrombins have a rapid onset of action, usually providing hemostasis within 10 minutes.\textsuperscript{9} They are effective for managing both localized and diffuse bleeding.\textsuperscript{30} Thrombins may be used alone or in conjunction with absorbable gelatin sponges.\textsuperscript{44–46} Using a thrombin with porcine gelatin may improve the efficacy of the latter because of the active role of thrombin in clotting.\textsuperscript{30} Because thrombins act on the final common pathway of coagulation, they may be useful for providing hemostasis in patients receiving antiplatelet agents or anticoagulants or with coagulopathies due to clotting factor deficiencies.\textsuperscript{9} Circulating fibrinogen is needed for thrombins to exert their hemostatic effects.\textsuperscript{29} Thrombins are moderately expensive compared with other local hemostatic agents.\textsuperscript{30}

Bovine thrombin was introduced in the late 1970s, and its efficacy is well established.\textsuperscript{9} Pooled human plasma-derived thrombin and recombinant human thrombin were introduced in 2007 and 2008, respectively, and are comparable to bovine thrombin in efficacy for achieving surgical hemostasis.\textsuperscript{59–61}

Bovine thrombin is available as a sterile powder that may be used as is (i.e., in dry form) or constituted with sterile 0.9\% sodium chloride.\textsuperscript{44} The constituted solution is stable for 8 hours at room temperature and 24 hours when refrigerated at 2\°–8\°C. The solution may be applied from a syringe (i.e., flooding the area with liquid), using an absorbable gelatin sponge immersed in the solution, or as a spray (the product is supplied in pump spray kits and syringe spray kits). Thrombins administered as sprays are particularly useful for managing diffuse oozing of blood and minor bleeding in large areas.\textsuperscript{9} Bovine thrombin and other thrombins do not need to be removed before wound closure.\textsuperscript{9} They should not be injected intravenously.\textsuperscript{44–46}

Pooled human plasma-derived thrombin is available as a lyophilized powder that is stable at room temperature for 8 hours after constitution with sterile water for injection.\textsuperscript{45} It also is available as a frozen solution that is stable after thawing for 24 hours at room temperature and up to 30 days under refrigeration.\textsuperscript{45} The solution is applied using a sterile syringe to flood the area or an absorbable gelatin sponge immersed in the solution. The product is not provided with a spray device.

Recombinant human thrombin is available as a lyophilized powder that is stable for 24 hours at room temperature after constitution with sterile 0.9\% sodium chloride. It is applied directly as a solution, an absorbable gelatin sponge soaked in solution, or a spray (the product is supplied in spray applicator kits with a spray pump, bottle, and syringe spray tip).

In a phase 3, randomized, double-blind study of 401 surgical patients, recombinant human thrombin was comparable in efficacy to bovine thrombin.\textsuperscript{60} Hemostasis was achieved within 10 minutes in 95\% of patients in each treatment group.

The amino acid sequence of bovine thrombin differs from that in human thrombin. Exposure to bovine thrombin is associated with a risk for immune-mediated coagulopathy because of the presence of small amounts of bovine clotting factors and the formation
of antibodies that cross react with and neutralize human clotting factors, especially clotting factor V and thrombin.\textsuperscript{62} The product labeling for bovine thrombin includes a black box warning about abnormalities in hemostasis ranging from asymptomatic alterations in laboratory test results to rare but potentially fatal severe bleeding or thrombosis due to immune-mediated coagulopathy.\textsuperscript{44} According to the product labeling for bovine thrombin, patients with antibodies to bovine thrombin should not be reexposed to the drug, although a laboratory test is not widely available to screen for these antibodies.\textsuperscript{44,63}

The development of antibodies to human clotting factors can occur in patients treated with pooled human thrombin or recombinant human thrombin, but the incidence of seroconversion is lower than that associated with bovine thrombin.\textsuperscript{59,60} Black box warnings about immune-mediated coagulopathy are not included in the product labeling for human thrombins. Whether differences in the development of antibodies translate into differences in the incidence of adverse events has been questioned.\textsuperscript{64,65} Improvements in the purity of the current formulation of bovine thrombin may reduce the risk for antibody formation compared with earlier formulations, although persistence of antibodies to bovine thrombin has been observed for up to 3 years after exposure.\textsuperscript{9,64,66} Adverse events from bovine thrombin reported to the FDA have decreased over the past two decades.\textsuperscript{67} Nevertheless, cases of immune-mediated coagulopathy continue to be reported, and cases may go unrecognized and unreported because of a lack of clinician awareness of the risk.\textsuperscript{52,66,68,69}

Pooled human thrombin is obtained from plasma donated at plasmapheresis centers.\textsuperscript{52} Donors are screened for prior exposure to certain viruses. Donated plasma is tested for the presence of certain viral infections (e.g., hepatitis B and C, human immunodeficiency virus, and parvovirus), and certain viruses are inactivated or removed during processing of donated plasma.\textsuperscript{45,67} No cases of transmission of infection in pooled human thrombin have been documented.\textsuperscript{52} Nevertheless, the product labeling for pooled human thrombin carries a warning about the theoretical risk of transmitting infectious agents, particularly viruses and prions.\textsuperscript{45} Creutzfeldt-Jakob disease, a rapidly progressive, fatal neurodegenerative disorder, is associated with a prion. In theory, bovine thrombin also may be associated with a risk for transmission of viruses and prions, but the manufacturing process appears to reduce this risk.\textsuperscript{52} The product labeling for bovine thrombin does not include a warning about a risk of transmitting infectious agents.\textsuperscript{44}

Recombinant human thrombin is produced through recombinant DNA technology using a Chinese hamster ovary cell line.\textsuperscript{46} Ecarin derived from snake venom is used in manufacturing of the product. Allergic reactions to hamster or snake proteins in the recombinant product are possible. The amino acid sequence of recombinant human thrombin is identical to that in human thrombin obtained from pooled plasma.\textsuperscript{66} A low rate of antibody formation to recombinant human thrombin has been observed.\textsuperscript{70} The safety of recombinant human thrombin in patients with antibodies to bovine thrombin and patients with previous exposure to recombinant human thrombin has been demonstrated.\textsuperscript{71,72}

FLOWABLE AGENTS

Flowable agents are paste-like mixtures of absorbable porcine or bovine gelatin particles in combination with thrombin for delivery to localized areas using a syringe-like applicator.\textsuperscript{29,32} The mixture conforms to irregular surfaces.\textsuperscript{10} The flowable agents promote hemostasis through passive and active mechanisms associated with gelatin and thrombin, respectively. They are used when conventional hemostatic measures are ineffective or impractical.\textsuperscript{32} Flowable agents are most effective for managing localized bleeding.\textsuperscript{30} The products may be more effective for managing bleeding than use of porcine gelatin sponges in combination with thrombin.\textsuperscript{33,34}

Flowable agents are relatively easy to prepare, requiring several minutes to form a paste by combining the gelatin particles with sterile saline or thrombin. Bovine gelatin particles are available with pooled human thrombin (Floseal). Porcine gelatin particles are available alone (Surgiflo hemostatic matrix) or in a kit that includes lyophilized human thrombin (Surgiflo hemostatic matrix kit).\textsuperscript{48,49} The former may be used in combination with bovine thrombin, pooled human thrombin, or recombinant human thrombin.\textsuperscript{30} The flowable products should be stored at room temperature and used promptly after preparation.\textsuperscript{47–49}
Safety concerns and precautions associated with flowable products include those associated with the components (e.g., risk for swelling and compression of surrounding tissues from gelatin, risk for allergic or immune reaction to materials from porcine or bovine sources, theoretical risk for transmission of viral or prion infection from pooled human thrombin). Flowable products tend to be costly compared with mechanical and active local hemostatic agents.  

**FIBRIN SEALANTS**

Fibrin sealants are two-component products for providing surgical hemostasis and occlusion when conventional surgical techniques are ineffective or impractical. These products provide fibrinogen and thrombin at the site of bleeding in larger concentrations than those ordinarily found in blood, which expedites conversion of fibrinogen to fibrin and clot formation. Fibrin sealants are effective for managing both localized and diffuse bleeding, but they tend to be costly compared with other local hemostatic agents. They were first used in the United States in the late 1990s.

Several fibrin sealant products with pooled human plasma containing fibrinogen and thrombin (Evicel and Tisseel) are available. The two components of Evicel are supplied in vials of frozen solution that are stable frozen for up to 2 years, 30 days under refrigeration, and 24 hours at room temperature. Thawing requires 10 minutes at 37°C (a higher temperature and longer duration at 37°C should be avoided), 1 hour at room temperature, and 1 day under refrigeration. The solution is sprayed or dripped in a thin layer on the bleeding site.

Evicel contains the fibrinolyis inhibitor aprotinin as well as fibrinogen and thrombin from pooled human plasma. Aprotinin is added to offset the fibrinolytic activity of plasminogen in Tisseel. A fibrinolyis inhibitor is not required in Evicel because of the manufacturing process, which removes plasminogen. Tisseel is supplied frozen in prefilled syringes and freeze dried in vials. The freeze-dried product requires constitution. The frozen product in syringes is premixed and ready to use after thawing, although it must be maintained at 33–37°C. The time required for thawing and stability depend on the package size and method used for thawing. Thawing can take as little as 5 minutes in a warm water bath, and the product must be used within 4 hours. By contrast, thawing can take an hour or longer at room temperature, and the product is stable for up to 48 hours. As with Evicel, Tisseel is applied as a thin layer by dripping or spraying the solution on the bleeding site. Safety concerns associated with these two products include the theoretical risk of transmission of infectious agents in pooled human thrombin. Anaphylactic reactions to aprotinin in Tisseel could occur.

A fibrin sealant (Vitagel) is available with a suspension of bovine collagen and bovine thrombin in syringes for mixing with autologous plasma. The patient’s plasma serves as a source of fibrinogen, which is converted to fibrin by bovine thrombin. The bovine collagen combines with fibrin to form a matrix and promotes platelet aggregation, degranulation, clotting factor release, and clot formation. The product may be more effective for providing hemostasis than bovine collagen alone. Preparation of Vitagel is complex and involves use of a cell packer and centrifuge. The syringes require refrigeration. The product is applied in a uniform coat using a cannula or spray. Safety concerns associated with this product relate to the use of thrombin and collagen from bovine sources (i.e., immune-mediated coagulopathy, allergic and immune reactions to bovine proteins). Because autologous human plasma is used as the source for fibrinogen instead of pooled human plasma from donors, the risk for transmission of viruses and prions may be reduced with use of this product instead of Evicel or Tisseel.

Pooled human plasma fibrinogen and thrombin integrated into absorbable patches are the two newest fibrin sealants—Tachosil equine collagen patches and Evarrest composite patches introduced in 2010 and 2012, respectively. The active side of the patches (yellow color for Tachosil, and powdery white-to-yellow color for Evarrest) contains fibrinogen and thrombin obtained from donated human plasma. The thrombin activates the fibrinogen at the site of application of the active side of the patch. Tachosil is approved by FDA for use in cardiovascular surgery when control of bleeding by standard surgical techniques (e.g., suture, ligature, cautery) is ineffective or impractical. Evarrest is approved by FDA for use with manual compression for soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and non-cardiac thoracic surgery when standard surgical methods of hemostasis are ineffective or impractical. Both patches are designed...
to be left in place, which facilitates the application of pressure to achieve hemostasis and is an advantage of the patches over liquid fibrin sealants.28 More than one patch may be used simultaneously, and the patches may be trimmed to fit the wound. Safety concerns with the use of these products include transmission of viral or prion diseases, although screening of plasma donors for risk factors for viral diseases and testing and treatment of the product to detect and reduce viral contaminants minimizes this risk.28 Allergy to equine proteins is a concern associated with Tachosil.53 Hypersensitivity reactions to Evarrest can occur.54 Neither patch requires special storage conditions (e.g., refrigeration), and both are ready to use. Tachosil patches are particularly costly. The cost of Evarrest patches remains to be determined.

OTHER LOCAL SEALANTS AND ADHESIVES

Synthetic polyethylene glycol (PEG) polymers (e.g., Coseal) are sealants that form a barrier to the flow of liquids, including blood.30 They are supplied as powders that are stored at room temperature and applied as liquids after constitution.73 The liquid quickly forms a hydrogel and provides hemostasis.32 Excessive swelling of PEG polymers can be problematic.32 The PEG polymer is absorbed and cleared by the kidneys, so the presence of renal impairment also is a concern.

A PEG polymer with human serum albumin (Progel) recently was introduced.28,74 Allergy to human albumin and renal insufficiency are concerns associated with its use. The PEG polymer component of Progel is supplied as a powder stored under refrigeration and constituted with saline no more than 20 minutes before application.28,74 This and other PEG polymer sealant products are costly.30

Bovine serum albumin plus glutaraldehyde (Bioglue) is a strong sealant with adhesive properties that promotes hemostasis in large blood vessels.30,32 It is supplied in a double-chambered syringe with various syringe tips.75 Cross linking of the aldehyde group of glutaraldehyde and lysine of albumin occurs within several minutes after assembly and priming of the syringe, so the product must be used promptly to avoid clogging of the syringe tips.32 Hypersensitivity, tissue necrosis, and adhesive embolism are among the safety concerns associated with this product.30 Bovine serum albumin plus glutaraldehyde is less costly than PEG polymer sealants.28

After reading this discussion guide, how would you rate your knowledge of: 1) blood products, 2) systemic hemostatic agents, and 3) local hemostatic agents?

☐ Greatly improved
☐ Somewhat improved
☐ Still inadequate

Cyanoacrylates have sealant and adhesive properties.28 Most of these products are used as adjuncts to surgical closure of skin incisions, not internally.32 A recently introduced product, octyl and butyl lactoyl cyanoacrylate (Omnex), is absorbable and used internally to seal blood vessels and provide hemostasis.28,76 It is provided as a liquid that is stored at room temperature and applied in a thin film using an applicator with a cannula tip.76 The sealant sets quickly, within approximately 5 minutes, so caution should be used to avoid contact with unintended tissues.76 Cyanoacrylates tend to be less costly than other local sealants and adhesives.28,30

Formulary Decisions

Considerations in selecting a strategy for managing perioperative bleeding include the type of surgical procedure; type and severity of bleeding; wound size, configuration, and accessibility; and patient characteristics (e.g., coagulation status).10,29 Small, discrete bleeding is managed differently from venous oozing from a large area.15 The local hemostatic product characteristics described in Table 2 (i.e., form, mechanism of action, and advantages and disadvantages in ease of preparation, method of application, efficacy, safety, and cost) influence the choice among available products for a specific patient.31 Formulary decisions about local hemostatic agents should take into consideration these differences in product characteristics. Duplication (i.e., inclusion of agents with the same mechanism of action and form) should be avoided or minimized. Input from surgeons as well as pharmacists who practice in critical care and surgical intensive care areas should be obtained when making formulary decisions because
surgeon experience with and preferences for specific products vary. Current sources of information should be consulted. The Appendix lists resources with information on achieving hemostasis in the operating room and critical-care setting.

Direct and indirect costs associated with the use of local hemostatic agents should be taken into consideration in making formulary decisions. Indirect costs include the cost of storing, preparing, and administering the product and reflect shelf-life and waste of products with limited stability. The costs for treating adverse events from local hemostatic agents and failure to provide prompt hemostasis (e.g., the costs for blood transfusion, extended hospital stays, rescue surgery for patients with recalcitrant bleeding, transfusion-related adverse events) as well as the acquisition cost should be considered. The potential impact of cost-reduction strategies, including bundling of multiple products from the same manufacturer as well as negotiation of favorable contract prices based on volume purchased, should be evaluated.

Local hemostatic agents can be costly for health systems. Surgeons should be encouraged to use less expensive mechanical agents for minor bleeding and reserve more costly local hemostatic agents for severe bleeding. Institutional guidelines for use of local hemostatic agents should be developed to reflect this strategy for containing costs without compromising patient care.

**Conclusion**

A wide variety of local hemostatic agents are available for use in providing surgical hemostasis. Differences among these agents in mechanism of action, ease of use, efficacy, safety, and cost should be taken into consideration in making formulary decisions that optimize use of these agents and patient outcomes.
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Assessment Test

This assessment test is provided here as a study aid only. Follow the instructions above to complete this assessment test and the evaluation online to obtain CE credit for this activity.

1. Which of the following is a risk factor for perioperative bleeding, blood transfusion, or both in surgical patients?
   a. Male gender
   b. Large body mass
   c. Autologous blood donation
   d. Advanced age

2. In the cell-based model for coagulation, which of the following phases is associated with the production of large amounts of thrombin, contributing to hemostasis?
   a. Initiation
   b. Amplification
   c. Priming
   d. Propagation

3. Which of the following is a systemic hemostatic agent that is potentially useful for reducing perioperative bleeding?
   a. Tranexamic acid
   b. Desmopressin
   c. Recombinant human thrombin
   d. Epoetin alfa

4. Which of the following is an advantage of most local hemostatic agents over systemic hemostatic agents?
   a. Lower cost
   b. Avoidance of systemic adverse effects
   c. Greater ease of administration
   d. Longer shelf-life

5. Which of the following local hemostatic agents provides an acid bactericidal environment that may reduce the risk of infection?
   a. Bovine collagen
   b. Porcine gelatin
   c. Oxidized regenerated cellulose
   d. Polysaccharide spheres

6. Recombinant human thrombin differs from bovine thrombin in its:
   a. Greater ease of preparation
   b. Greater ease in application as a spray to large areas of bleeding
   c. Lower risk for development of antibodies to human thrombin and clotting factor V
   d. Greater efficacy in controlling bleeding

7. Which of the following is a potential advantage of flowable agents over most other local hemostatic agents?
   a. Greater usefulness for irregular bleeding surfaces
   b. Lower cost
   c. Lower risk for swelling and compression of surrounding tissues
   d. Lower risk for allergic/immune reaction to foreign proteins

8. Which of the following is an advantage of patches containing pooled human plasma fibrinogen and thrombin over other fibrin sealants?
   a. Greater ease of use without preparation
   b. Lower cost
   c. Lower risk for transmission of viruses and prions
   d. Lower risk for allergic/immune or hypersensitivity reaction
9. Which of the following local hemostatic agents is the most complex to prepare and use?
   a. Polysaccharide spheres in a bellows applicator
   b. Oxidized regenerated cellulose sheets
   c. Bovine thrombin sterile powder
   d. A fibrin sealant containing bovine collagen and bovine thrombin with autologous human plasma

10. Which of the following types of local hemostatic agents generally is least costly?
    a. Mechanical
    b. Active
    c. Flowable
    d. Fibrin sealant

11. Which of the following reflects bundling of local hemostatic agents as a cost-reduction strategy by health systems?
    a. Purchase of a large quantity of a single product
    b. Purchase of multiple products from the same manufacturer
    c. Purchase of combination products instead of separate ingredients
    d. Negotiation of rebates as well as discounted prices

Appendix. Resources on Achieving Hemostasis in the Operating Room and Critical-Care Setting

American Society of Health-System Pharmacists
www.ashpadvantage.com/hemostasis
- Multifaceted educational initiative for health-system pharmacists on achieving hemostasis in the operating room and critical care setting
- Regional presentations and webinars on what the pharmacist needs to know

The Joint Commission
www.jointcommission.org
- Online calculator to predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables (available at www.sts.org/quality-research-patient-safety/quality/risk-calculator-and-models)


