Clinical and Pharmacoeconomic Evaluation Of Thrombin-Containing Products In the Hospital Setting

**Statement of Need**
Postoperative bleeding can be a multifactorial consequence of any surgical procedure and is associated with increased morbidity and mortality. Many hemostatic methods and products are used in the management or prevention of bleeding— including transfusion of blood products and administration of various pharmacologic agents, such as topical thrombins of bovine, human, and recombinant origins. Complexities in the selection and use of topical thrombins are substantial. Evidence and practice gaps are acknowledged, as are associated performance issues, underscoring the need for continuing clinical education in this area. Primary and qualitative data suggest that surgeons, pharmacists, and nurses largely are unaware of the risks for and pathophysiology of postoperative-induced coagulopathy with the use of bovine thrombins, as well as the availability, clinical profiles, active components, and pharmacoeconomic considerations of newer thrombin products. The precise incidence of such coagulopathies is not known and likely is underestimated. This may be due, in part, to poor documentation of thrombin use—as these products may enter institutions via central surgical supply rather than the pharmacy department —and may result in delayed recognition and diagnosis of potentially catastrophic complications. In the absence of a commercially available laboratory test to detect bovine thrombin antibodies, clinicians must exercise vigilance in selecting topical thrombins and would benefit from multidisciplinary education on the mechanisms of coagulation and coagulopathy, differential clinical profiles of topical thrombins, and safe use of hemostatic agents.

**Learning Objectives**
At the completion of this activity, participants should be better able to:
- Analyze the clinical and economic effects of bleeding in the surgical setting, especially as they pertain to the management of acquired postoperative coagulopathy.
- Describe key mechanisms that may underlie the development of acquired postoperative coagulopathy.
- Assess relevant risks and benefits of topical thrombins for achieving hemostasis.
- Devise an inventory of considerations (eg, active components, clinical profiles, and pharmacoeconomic impact) by which topical thrombins should be evaluated, acquired, and used in the hospital setting.

**Target Audience:** Physicians, pharmacists, and nurses

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**Financial Disclosures**
Paul M. Ness, MD: ZymoGenetics (consultant); Caridian BCT (advisory committee).
Mark A. Malesker, PharmD: Sanofi-aventis, ZymoGenetics (speakers’ bureaus); Sanofi-aventis, ZymoGenetics (advisory committees).
William D. Spotnitz, MD, MBA: Nothing to disclose directly (Active agreements are between the University of Virginia and Baxter, Bayer, Johnson & Johnson, LifeBond, Neomend, ProFibrik, and ZymoGenetics for consultation, speaking, advising, education, review of research plans).
Mary Culpepper: Nothing to disclose.

**Disclosure of Unlabeled Use**
This educational activity may contain discussion of some agents that have been studied but are not FDA-approved for use as hemostatic agents. Please refer to official prescribing information for all products for discussion of approved indications, contraindications, and warnings.

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Introduction

Despite advanced technologies and meticulous surgical technique, perioperative bleeding remains a troublesome surgical complication, associated with increases in morbidity and mortality, hospital length of stay (LOS), multiorgan failure, and risk for infection.1, 2 Cardiac surgeries, in particular, are associated with excessive perioperative blood loss—in as many as 14% of cases.2 Bleeding also carries the potential for excessive blood product transfusion, for which a growing evidence base suggests inferior surgical outcomes.1, 4-6 Although safety improvements have reduced risks for transfusion-transmitted infectious diseases, concerns remain about the potential for the hazards of blood product transfusion—such as mistransfusion, cardiopulmonary toxicity, acute lung injury, graft-versus-host disease, and metabolic derangements from stored blood.7-9

Reducing blood loss is an important surgical goal, pursued with a variety of strategies (Table 1), including adjunctive hemostats such as thrombins, to control active localized or diffuse surgical bleeding.10 These agents are used with increasing frequency in a surgical environment that favors minimally invasive (eg, laparoscopic, endoscopic, robotic) surgical technologies that, although generally associated with lower risk for overall bleeding compared with open surgery, increase the likelihood of nonsuturable, noncauterizable bleeding.10 In the United States, an estimated $250 million is spent annually on topical thrombins in more than 1 million surgeries,2,11,12 and the growing use of minimally invasive technologies in the approximately 46 million inpatient surgical procedures performed annually13 is expected to drive that rate higher.13-15 Within this context, a review of the relative efficacy, safety, ease of use, and costs of thrombins is appropriate.

Thrombin in the Coagulation Cascade

Thrombin, also known as activated factor II, is a clotting factor and serine protease with a critical role in physiologic hemostasis. Thrombin controls the final step of coagulation, which represents the conclusion of a series of intrinsic mechanisms and promotes hemostasis.2,11,16 The process is complex, requiring coordinated signal transduction and activation of platelets and plasma clotting factors (primary hemostasis) and resulting in the formation of a stable, cross-linked, platelet–fibrin clot (secondary hemostasis).16,17 Thrombin converts soluble fibrinogen into fibrin, a glycoprotein that forms an insoluble matrix that is sealed by factor XIII in the final stage of coagulation.16,17 Thrombin also activates protein C (a coagulation inhibitor) and factor V.11

An important cofactor in prothrombin activation, factor V plays a central role in coagulation (Figure 1).19 It is active at the convergence of the extrinsic and intrinsic coagulation pathways, a junction of clinical importance; thrombin generation can be disrupted profoundly by any substance or event that inhibits factor V.17,19 It also is pivotal in activating factor X, which converts prothrombin to thrombin. Platelet-mediated activation of factors V, VIII, and XI amplifies thrombin generation.2,18,20 Thrombin is used surgically as an active hemostat to convert fibrinogen to fibrin at the site of active bleeding.10

Overview of Available Topical Thrombins

Effectiveness and ease of use have made thrombin products a mainstay in cardiovascular (CV), orthopedic, neurologic, gynecologic, and other surgeries in which conventional methods of hemostasis are insufficient to control bleeding. Topical thrombins of 3 distinct biologic origins (bovine, human, recombinant) are available (Table 2).21-23 Bovine-derived thrombin has been used clinically since the 1940s and was the only type of topical thrombin commercially available until human pooled-plasma thrombin was approved by the FDA in 2007. Recombinant thrombin was approved in 2008. All of the thrombins have equivalent efficacy, as demonstrated by randomized controlled clinical studies that compared either human or recombinant thrombin to bovine thrombin.24,25 All thrombins also had similar and manageable adverse event (AE) profiles.24,25 All are labeled as aids to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessable, and all are indicated for use with an absorbable gelatin sponge.21-23

Thrombin concentration correlates with reaction rate—the speed at which thrombin causes clot formation; all 3 types are available at a concentration of 1,000 units/mL. Thrombins often are used in conjunction with other hemostats as shown in Table 1. For example, fibrin sealants polymerize fibrinogen into fibrin and form a sealing barrier whether or not bleeding is present.10 Freestanding thrombin products may be combined with several materials and used 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 thrombins and can result in extensive clotting, hypotension, and even death.21-23

Surgical scenarios amenable to the use of thrombin include diffuse raw surface bleeding, bleeding from needle holes (such as in a peripheral arterial bypass with graft), and circumstances in which cauteration would compromise continuity of the surgical anastomosis.

Clinical Experience With Topical Thrombins

Bovine Thrombin

The most extensive clinical experience is with the use of bovine thrombin, which in various forms has been used for more than 70 years. Several bovine-derived thrombin formulations and products have been available, but currently only one is marketed in the United States.21 It
that may follow the use of this product.27,30

of bovine thrombin postoperative coagulopathies, clinicians should

tially serious coagulopathies.21 Bovine thrombin is the only product

based on concerns about the possibility for development of poten-
ties to bovine thrombin should not be re-exposed to the product

thrombin labeling stating that patients with established antibod-

dies.2,9,28,29 In 1996, the FDA added a boxed warning to bovine

exposure may increase patient risk for postoperative coagulopa-

tion in one or more elements of inherent clotting mechanisms). 2,27

Immune-mediated coagulopathy (IMC)—the precise incidence

of which is unknown—may develop as a result of the formation

of antibodies against contaminating bovine coagulation proteins

(such as factors V and Va) or development of human coagulation-

protein antibodies that may cross-react with factor V, thrombin, or

both.18,27 Clinical manifestations of IMC can range from altered

coagulation parameters (eg, prothrombin time [PT], activated par-

thrombin time [aPTT], international normalized ratio [INR], and thrombin time [TT]) to clinically severe bleeding,

which rarely can be fatal.11,18,19,27-29

The presence of anti-bovine thrombin antibodies prior to re-

exposure may increase patient risk for postoperative coagulopa-
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thrombin labeling stating that patients with established antibodies

to bovine thrombin should not be re-exposed to the product

based on concerns about the possibility for development of poten-
tially serious coagulopathies.31 Bovine thrombin is the only product

in its class to have a boxed warning. Although it has been shown to

produce a greater immunogenic response than human or recombi-
nant thrombins, evidence supporting a significantly increased clini-

cal risk for postoperative complications with the use of this product

is insufficient. Since 2008, bovine thrombin manufacturing has

incorporated chromatic purification and ultrafiltration processes

that substantially reduce—but do not completely eliminate—factor

V content (<92 ng/mL).21 The clinical implications of these mea-

ures are unknown.21 Despite limited evidence regarding the effects

of bovine thrombin postoperative coagulopathies, clinicians should

be vigilant for possible acquired factor-associated coagulopathies

that may follow the use of this product.27,30

is produced through a conversion reaction in which prothrombin of

bovine origin is activated by tissue thromboplastin in the presence

of calcium chloride. Subsequent to FDA approval in the 1970s, interest

in and use of topical thrombin have continued to increase.11,18 Com-
pared with earlier products that contained 20% to 30% thrombin, the

currently available product, approved in 1995, contains fewer protein

contaminants and has been shown to be 96% thrombin.21,26

Despite its clinical effectiveness, bovine thrombin has been associated with a relatively uncommon coagulopathy (ie, dysfunc-
tion in one or more elements of inherent clotting mechanisms).2,27

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of which is unknown—may develop as a result of the formation

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Human Thrombin

Purified human pooled-plasma thrombin is made from pooled human-
source and recovered plasma obtained from FDA-licensed plasmaphere-
sis centers.22 Human thrombin is manufactured by chromatographic

purification of prothrombin from cryo-poor plasma followed by activ-
tion with calcium chloride. The product undergoes rigorous pathogen-

reduction measures, including targeted steps of solvent detergent cleansing,
vapor heat treatment, and nanofil-

tration for inactivation or removal of

viruses.22 Despite these measures, the

FDA recognizes at least a small risk for transmitting infectious agents

such as viruses and theoretically, the

Creutzfeldt-Jakob disease agent.22,31

Hepatitis A and parvovirus B19 are

particularly difficult to remove or

inactivate, as is described in patient counseling information.22

Human pooled-plasma thrombin was shown in a Phase III, pro-
spective, randomized controlled, double-blind study to be as effect-

ive as bovine thrombin.25 In the multicenter study with a primary
efficacy end point of hemostasis at 10 minutes, Doria et al randomized

305 patients undergoing CV, neurologic, or general surgeries to

receive either bovine (n=152) or human (n=153) thrombin admin-

istered with an absorbable gelatin sponge. Individuals with known

antibodies to bovine thrombin were excluded. In both groups, 97.4%
of subjects achieved hemostasis at 10 minutes. AEs in both groups

were similar and as expected for the procedures, the most common

being pruritus. At least one serious AE was reported in 17% of sub-

jects who received human thrombin and 11% of those who received

bovine thrombin. Only 1.3% of serious AEs were possibly, probably,
or definitely related to thrombin administration. 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).

Recombinant Thrombin

Recombinant human thrombin is derived from Chinese ham-
ster ovary (CHO) cell cultures and uses enzymes derived from snake

venom to activate prethrombin-1 to α-thrombin,2,23,32 resulting in a

molecule very similar to human thrombin in amino acid sequence and

structure.21 CHO cell lines are used in numerous recombinant prod-

ucts including human insulin and human factors VIII and VIIa. The

FDA recognizes recombinant thrombin as being free of known infec-
tious agents or risks for viral or prion disease transmission, although

the manufacturer is conducting a requested study to assess the safety

of re-exposure to recombinant thrombin. The relatively low immuno-
genicity profile of recombinant thrombin eliminates the potential for

antibody formation or cross-reaction. However, some patients may be

at risk for allergic reactions to hamster or snake proteins with the use

of this product.23

A Phase III, double-blind, randomized comparative study demon-

strated equivalent efficacy and tolerability for recombinant thrombin

compared with bovine thrombin.24 In the study by Chapman et al,

Figure 1. Role of thrombin in hemostasis.19

![Figure 1. Role of thrombin in hemostasis.](image-url)
Table 2. Active Topical Thrombins21-23

<table>
<thead>
<tr>
<th>Biologic Origin</th>
<th>How Supplied</th>
<th>Storage</th>
<th>Warnings, Contraindicationsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine21</td>
<td>Powder for solution 5,000-IU vial + 5-mL diluent</td>
<td>2°C to 25°C unopened</td>
<td>Black box warning</td>
</tr>
<tr>
<td></td>
<td>20,000-IU vial + 20-mL diluent</td>
<td>2°C to 8°C for ≤24 h after</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20,000-IU kit + spray pump, actuator</td>
<td>reconstitution</td>
<td>Do not inject</td>
</tr>
<tr>
<td></td>
<td>20,000-IU kit + spray tip, syringe</td>
<td>Room temperature for ≤8 h</td>
<td>Antibody formation, hemostatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>after reconstitution</td>
<td>abnormalities</td>
</tr>
<tr>
<td>Human22</td>
<td>Frozen solution 2-20 mL vials (800-1,200 units/mL)</td>
<td>Frozen (≤−18°C) for ≤2 y</td>
<td>Hypersensitivity to material</td>
</tr>
<tr>
<td></td>
<td>Device kit containing lyophilized powder for</td>
<td>2°C to 8°C for ≤30 d</td>
<td>of bovine origin</td>
</tr>
<tr>
<td></td>
<td>reconstitution, use with gelatin sponge</td>
<td>unopened</td>
<td></td>
</tr>
<tr>
<td>Recombinant23</td>
<td>Powder for solution 5,000-IU vial + 5-mL prefilled</td>
<td>2°C to 25°C unopened</td>
<td>Do not inject</td>
</tr>
<tr>
<td></td>
<td>diluent syringe</td>
<td>2°C to 25°C for ≤24 h after</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20,000-IU vial + 20-mL diluent syringe</td>
<td>reconstitution</td>
<td>Massive or brisk arterial</td>
</tr>
<tr>
<td></td>
<td>Spray Applicator Kit containing 20,000-IU vial</td>
<td></td>
<td>bleeding</td>
</tr>
<tr>
<td></td>
<td>spray pump, spray bottle, syringe, bowl, 2 blank</td>
<td></td>
<td>Anaphylactic or severe</td>
</tr>
<tr>
<td></td>
<td>labels</td>
<td></td>
<td>systemic reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>to human blood products</td>
</tr>
</tbody>
</table>

IU, international unit

a All pregnancy category C; either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

411 adults undergoing hepatic resection (n=125), spinal surgery (n=122), peripheral arterial bypass surgery (n=88) or arteriovenous graft formation for hemodialysis access (n=76) were randomized to receive either recombinant (n=205) or bovine thrombin (n=206); 401 patients completed the study. Both agents were applied with an absorbable gelatin sponge; the primary efficacy end point was hemostasis at 10 minutes. In both treatment groups, 95% of subjects achieved end point (bovine thrombin, 95.1%; recombinant thrombin, 95.4%). Incidence of AEs was similar for the 2 groups, with most reported AEs being as expected and moderate in severity.

A significantly lower incidence of antibody formation and lower frequency of cross-reacting antibodies has been observed with the administration of recombinant thrombin compared with that of bovine thrombin. In the Chapman study, 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 2). Antibody development was not associated causally with any AEs, such as excess bleeding, in either treatment group. The clinical implications of minimal immunogenicity are yet to be seen, and available data on repeat exposure to recombinant thrombin are limited.

**Recognition and Management of IMC**

Perioperative coagulopathy is a serious surgical complication with potentially catastrophic consequences. Causes may include therapeutic anticoagulation (ie, with heparin or warfarin) or irreversible platelet inhibition (eg, with aspirin or another antplatelet agent), acidosis, enzymatic dissolution of fibrin (eg, fibrinolysis) related to cardiopulmonary bypass, heparin-induced thrombocytopenia, liver dysfunction, disseminated intravascular coagulation (DIC), inactivation or dissolution of fibrinogen in the blood (fibrinogenolysis), consumptive loss of coagulation factors, hypothermia, or other mechanical and metabolic derangements. Coagulopathies may be hemorrhagic or thrombotic; inherited (eg, hemophilia, von Willebrand disease); or acquired (eg, vitamin K deficiency, liver disease, immune-mediated).

Bovine thrombin-associated IMC has been recognized for more than 20 years as a distinct type of acquired coagulopathy despite low clinical awareness, particularly among surgeons. A study by Ortel et al was the first to define immunologic response prospectively in individuals exposed to bovine thrombin during CV surgery. A seropositive immune response was detected in 94.3% of patients exposed to the thrombin, with antibody formation in response to at least one bovine coagulation protein. In this group, most patients developed antibodies specific for bovine factors V and Va (80.7% and 90.7%, respectively); 20% also developed antibodies to bovine thrombin. Among subjects exposed to thrombin, 51% also developed antibodies that cross-reacted with their own human coagulation proteins. Among those with prior exposure to bovine thrombin, 33% had detectable preoperative antibodies to 2 or more bovine antigens, and those with antibodies to multiple bovine proteins were 5 times more likely to experience clinical complications.

Reported incidence rates for the development of antibodies in response to bovine thrombin exposure range from 10% to 90%; recent studies using purer forms of bovine thrombin have found incidence rates of 12.7% to 27%, suggesting an actual incidence at the lower end of the range. Variability likely is influenced by surgery type, history of prior exposure, and purity of the thrombin preparation. Factor V antibodies develop in 40% to 60% of cardiac surgery patients compared with 20% of neurologic surgery patients. Prior exposure to bovine thrombin may confer an 8-fold increase in likelihood of antibody development. In one review, 33% of 58 patients with bovine thrombin-associated antibodies developed bleeding complications, 6% of which were fatal.
The recognition of bovine thrombin-associated IMC poses unique clinical challenges, particularly with subtle presentations (eg, nosebleed) or late-onset bleeding that begins after hospital discharge. In fact, the median time to clinical presentation or laboratory abnormality is 11 days. Presentations may vary, can be masked by other conditions, and may or may not be associated with bleeding. A literature review of 64 cases reported near-equal representation of bleeding and nonbleeding presentations. In addition, no assay to detect immunologic response to bovine thrombin is licensed and available for clinical use. In an asymptomatic patient, the only manifestation may be alterations in laboratory coagulation parameters.

Prior exposure to bovine thrombin has been identified as the most common causal factor in the development of IMC; documentation of such exposure may be unavailable, however, because thrombin may have been used as a stand-alone product or a component of a flowable or fibrin sealant. Moreover, it may enter hospitals via central surgical supply rather than being purchased through the pharmacy department, and often it is not documented in a patient’s medical records because its use is common. Thus, a patient’s history of previous surgery in which bovine thrombin likely was used (eg, multiple cardiac, pediatric, neurologic, or vascular surgeries or burn debridements) may provide the best clue.

IMC should be included in differential diagnoses in patients with unexplained postoperative bleeding; hemoptoma not caused by hemodilution, DIC, vitamin K deficiency, or thrombocytopenia; unexplained PT, aPTT, or TT in the absence of bleeding (which may be detected upon a patient’s return for follow-up or in preparation for additional surgery); exaggerated response to postoperative anticoagulation; or bleeding that is unresponsive to conventional treatment. If a mixing study (1:1 mix of patient plasma with normal pooled plasma) fails to correct, an inhibitor should be suspected, a hematology consult requested, and specific quantitative factor assays of factor V and factor V inhibitor conducted.

The clinical consequences of IMC can be severe even if bleeding is not present; coagulation studies are costly and time-consuming, and prolonged clotting time may delay therapeutic procedures. The Joint Commission has called bovine thrombin-associated IMC a threat to patient safety and urged greater clinician awareness about this iatrogenic and preventable complication. Large-scale evidence to guide the management of IMC is limited, however. In an asymptomatic patient with a detectable coagulopathy, a reasonable approach is administration of vitamin K or fresh frozen plasma and close observation, if surgery is not required emergently. Immunosuppression should be considered if high inhibitor levels are detected. More problematic is the nonbleeding patient requiring surgery, for whom an appropriate strategy is to treat the inhibitor with a goal of reversal. Therapeutic choices are difficult in the case of a bleeding IMC. Platelets may be the most rational course because of the store of factor V on their surface, although treatment approaches are speculative and patient-specific. Based on review of case reports, plasma and activated plasma components such as factor VIIa (recombinant), which requires an intact common coagulation pathway, are not recommended for the management of a bleeding IMC. Chemotherapy or immunosuppressive drugs such as prednisone may be useful, and there is limited experience with plasmapheresis. Prolonged hospitalization for supportive care is the most common intervention for patients with IMC and active bleeding or risk for bleeding.

Overall, according to the FDA’s Adverse Event Reporting System for January 1986 to December 2006, spontaneous reports of bovine thrombin-related AEs occur at very low rates, and bleeding coagulopathies were reported only with products approved prior to 1995.

The analysis, published in 2010, is not powered to measure associations or causation, but it may indicate a lack of reporting in larger follow-up trials or reduced amounts of immunogenic contaminants in bovine thrombin.

### Pharmacoeconomic Considerations

Cost-effectiveness is an important consideration in evaluating topical thrombins. Pricing is competitive for products of all 3 biologic origins. Average wholesale prices (AWPs) in 2010 for a 20,000-IU vial of bovine or recombinant thrombin were $323 and $413, respectively; the AWP for a 20-mL vial of human plasma-pooled thrombin was $375. However, acquisition costs vary by institution and are influenced by factors such as contract pricing, purchasing group criteria, and volume usage. In terms of direct costs for surgical hemostats, topical thrombins are moderate in cost. Generally, a topical thrombin is less costly than a flowable product and somewhat more costly than a mechanical agent. A fibrin sealant generally is the most expensive.

A number of nonmedication costs—preparation, mixing, storage, administration, and potentially coagulation monitoring—should be considered in a pharmacoeconomic evaluation of thrombins. Thus, a direct cost-minimization analysis model may not be the most effective method of comprehensive institutional cost evaluation for these agents, despite their equivalent efficacy. The potential for complications should be reviewed, as should medical–legal concerns that could result from errors of use and organizational attitudes regarding safety issues, such as protocols for medications with boxed warnings. Waste reduction is another consideration. A recent 9-month university hospital study recently examined a switch from bovine thrombin 20,000-IU vials with spray applicators to recombinant thrombin 5,000-IU vials with or without a spray kit in 559 surgical cases. Dual primary end points were usefulness/clinician acceptance and thrombin usage. 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. Average per-case consumption decreased from a 20,000-unit bovine thrombin spray kit to 13,500 units of recombinant thrombin; use of 1 or 2 vials was sufficient for 68% of cases.

**Figure 2. Recombinant vs bovine thrombin: antibody development.** No adverse events causally associated with antibody formation in either group.
A Case of Postoperative Hemorrhagic Shock\textsuperscript{55}

The patient, a 76-year-old woman, developed severe hemorrhagic complications after surgical exposure to bovine thrombin. Course as follows:

**Initial diagnosis DIC with coagulopathy**

**Resolution of DIC, continuing hemorrhages**

Positive mixing studies
- Clotting factor assays showed significantly reduced factor V activity (<5% of normal) that confirmed IMC
- Inhibitor titer assay confirmed factor V inhibitor

**Patient required critical care hospitalization of 64 days**

- Blood product transfusions (282 units)
- 2 reoperations for hemorrhage
- **Total estimated costs of hospitalization, blood products alone >$440,000**
- Costs not factored in: consultations, reoperations, imaging studies, laboratory tests, other therapeutic interventions, patient transfer

Conventional cost-effectiveness modeling for the management of IMC is not feasible because the precise incidence is not known. However, quantifiable resource utilization costs may be considerable in even a single case, which may increase hospital LOS by a factor of 2 to 2.5 if transfusion of blood product is required.\textsuperscript{55,56} Costs of hospitalization and blood products alone in the management of an IMC have been reported to be as high as $440,000 (sidebar).\textsuperscript{55} An economic impact review found estimated median treatment costs of IMC to be $56,668 (range, $16,584-$129,828) for nonbleeding complications, ensuring cautionary labeling of syringes used in reconstitution of thrombin (ie, “do not inject”), and safe handling and segregation of sound-alike medication errors, recognizing potential complications. Appropriately, drug class-specific information on reduced antigenicity of relatively more pure thrombin products will result in a reduced incidence of IMC. Because of the potential for adverse immunologic reactions, the practice guideline issued jointly by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists recommends against the use of bovine thrombin in cardiac surgery procedures.\textsuperscript{9}

**Conclusion**

Thrombin preparations from all 3 biologic sources have been shown in prospective studies to have comparable direct costs, efficacy, and safety. Known risks for viral or disease transmission are higher for human pooled-plasma thrombin than for recombinant thrombin, and known risks for the development of cross-reacting antibodies are higher for bovine thrombin than for recombinant thrombin. Case reports of immunologic reactions to bovine proteins have helped quantify resource utilization costs of treating IMC, a complication that develops with greater frequency after exposure to bovine thrombin compared with human or recombinant thrombin. Cross-reacting antibodies are implicated in the development of IMCs, which are clinically heterogeneous, difficult to diagnose, costly to manage, and may be underrecognized. In patients with previous exposure or known antibodies to bovine thrombin, human or recombinant thrombin may be reasonable alternatives for surgical hemostasis. In the absence of prospective studies that might clarify unanswered questions about whether lower incidence of cross-reacting antibodies associated with the use of recombinant thrombin is associated with lower incidence of IMC, surgeons and pharmacists should be aware of the many issues surrounding the selection and use of thrombins in surgical settings.

**References**

1. Thrombin products achieve a local hemostatic effect by ___.
   a. converting fibrinogen into fibrin  
   b. forming a hydrogel that seals tissues  
   c. acting as a mechanical matrix for clot formation  
   d. promoting platelet degranulation

2. ___ is contraindicated with the use of all topical thrombin products.
   a. Hypersensitivity to hamster proteins  
   b. Anaphylactic or severe systemic reaction to human blood products  
   c. Direct injection into the circulatory system  
   d. Hypersensitivity to material of bovine origin

3. Which statement about topical thrombin products is true?
   a. All undergo rigorous antiviral processing.  
   b. None requires thawing.  
   c. All have equivalent efficacy.  
   d. All are available at a concentration of 125 IU/mL

4. Cross-reacting antibody formation is associated with the use of which thrombin most frequently?
   a. Bovine-derived thrombin  
   b. Recombinant thrombin  
   c. Human pooled-plasma thrombin  
   d. All thrombins are associated with equivalent immunogenic responses

5. Which of the following statements about factor V is true?
   a. Inhibition of factor V can disrupt thrombin generation and impair coagulation.  
   b. Factor V is active in the extrinsic pathway of the coagulation cascade.  
   c. Specific factor V antibody assays are readily available for commercial use.  
   d. Thrombin-associated factor V deficiencies generally are corrected rapidly by mixing studies.

6. The most prevalent intervention for patients with bovine thrombin-induced immune-mediated coagulopathies (IMCs) is ___.
   a. prophylactic therapy to prevent bleeding  
   b. immunosuppressive therapy  
   c. chemotherapy  
   d. extended length of hospitalization

7. In the absence of a conclusive determination through documentation in medical records, ___ might strongly suggest prior patient exposure to bovine thrombin.
   a. the development of thrombocytopenia  
   b. prior blood product transfusion  
   c. multiple prior cardiac, neurologic, or vascular surgeries  
   d. documented use of therapeutic anticoagulation

8. At home 2 weeks after bilateral hip replacement surgery, a 72-year-old man develops a nosebleed. Which of the following may be associated with elevated clotting times?
   a. Recombinant thrombin  
   b. Active, flowable, or fibrin sealant hemostats  
   c. Oxidized regenerated cellulose  
   d. Human pooled-plasma thrombin

9. Quantifiable resource utilization costs for the management of IMC may be doubled in clinical scenarios in which ___.
   a. transfusion of blood product is required  
   b. coagulation studies are inconclusive  
   c. vitamin K deficiency is detected  
   d. the patient has history of multiple neurologic surgical procedures

10. In the case report described on page 6, the 2 significant economic costs factored into managing a bovine thrombin-associated IMC were:
   a. therapies directed at an initial diagnosis of disseminated intravascular coagulation  
   b. consultations, imaging studies, and 2 reoperations  
   c. coagulation mixing studies to confirm a diagnosis of IMC  
   d. extended critical care hospitalization and blood product transfusions
Answer Sheet and Evaluation Form

Clinical and Pharmacoeconomic Evaluation of Thrombin-Containing Products in the Hospital Setting

Release Date: November 1, 2010 Expiration Date: November 1, 2011

Participate online at: CMEZone.com Type MN109 in the keyword field (availability may be delayed from print date).
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City: ___________________________________________________________________ State: _______________ ZIP: _____________________________
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☐ Physician  I am claiming _____ AMA PRA Category 1 Credit™  ☐ Pharmacist  ☐ Nurse
☐ Other (specify): ______________________________________________________________________________________________________________

Evaluation Questions

Please answer the following questions by circling the appropriate rating.
4 = Strongly Agree  3 = Agree  2 = Disagree  1 = Strongly Disagree

1. After participating in this activity, I am better prepared to:
   a. Analyze the clinical and economic effects of bleeding in the surgical setting, especially as they pertain to the management of acquired postoperative coagulopathy. 4 3 2 1
   b. Describe key mechanisms that may underlie the development of acquired postoperative coagulopathy. 4 3 2 1
   c. Assess relevant risks and benefits of topical thrombins for achieving hemostasis. 4 3 2 1
   d. Devise an inventory of considerations (eg, active components, clinical profiles, and pharmacoeconomic impact) by which topical thrombins should be evaluated, acquired, and used in the hospital setting. 4 3 2 1

2. The activity met my educational needs. 4 3 2 1

3. The faculty were knowledgeable and effective in the presentation of content. 4 3 2 1

4. The teaching method and educational materials were effective. 4 3 2 1

5. The learning activities were effective and incorporated active learning methods. 4 3 2 1

6. The post-test accurately assessed learning. 4 3 2 1

7. The content was objective, current, scientifically based, and free of commercial bias.
   ☐ Yes  ☐ No (please explain): ____________________________________________________________________________________________

8. Based on information presented in this activity, I will:
   ☐ do nothing, as the content was not convincing.
   ☐ seek additional information on this topic.
   ☐ change my practice.
   ☐ do nothing, as current practice reflects the program’s recommendations.

9. The most important concept learned during this activity that may effect a change in patient care is: ____________________________________________________________ ____________________________________________________________ ____________________________________________________________ ____________________________________________________________

10. What issue(s) related to the therapeutic area discussed in this activity, or other topics, would you like addressed in future continuing education?
    ______________________________________________________________________________________________________________________________________________________
    ______________________________________________________________________________________________________________________________________________________
    ______________________________________________________________________________________________________________________________________________________

11. Additional comments: ________________________________________________________________________________________________________________________________________________________________________________________________________________________

Post-Test Answer Section

Please circle the correct answer for each question. (A score of at least 70% is required to receive credit.)

1. a b c d
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d
8. a b c d
9. a b c d
10. a b c d