Hemorrhage is a leading cause of preventable morbidity and mortality in and out of the operating room. Surgical bleeding can have a significant impact on both patient outcomes and health care costs. Poor hemorrhage control is strongly linked with untoward outcomes and drives clinicians to use treatment methods that may further lead to increased morbidity and mortality. Adverse events related to bleeding and blood transfusion are dose-dependent, with increased transfusion rates associated with higher morbidity. A retrospective analysis of more than 1 million surgical procedures of varying types found that bleeding-related surgical complications occurred in 29.9% of patient operations, translating into a 6-day average increase in hospital length of stay. In this study, increases in hospitalization costs related to bleeding-related complications ranged from $2,805 (in reproductive organ surgery) to $17,279 (in spinal surgery). At least 3 factors have an impact on bleeding-related complications: progressively widespread use of anticoagulant and antiplatelet therapeutics; technologic advances that enable complex and lengthy surgical procedures; and the advancing age of the general population, with associated comorbidities that predispose to bleeding-related complications. Recognition of the importance of bleeding-related complications has resulted in an explosive use of topical hemostatic adjuncts throughout the health care environment. Available preparations of topical hemostatic adjuncts include a host of formulations and significant differences between products. Products vary with regard to efficacy, reproducibility of action, and safety. As a result, a bewildering array of products confronts clinicians faced with hemorrhage in and out of the operating room. Consequently, a standardized method that would allow rational application of topical hemostatic agents would be beneficial to both clinicians and their patients. In order to bridge the knowledge gap between product design mechanisms and clinical applicability, the Society for the Advancement of Blood Management (SABM) convened a multidisciplinary panel of physicians, nurses, allied health professionals, pharmacists, and hospital administrators involved in patient blood management to address important aspects of topical hemostatic agents. The goals of this gathering included identification of unmet needs spanning the knowledge gap in the current use of topical hemostatic therapy in the surgical setting, and the offer to clinicians of a guide for understanding this complex array of therapeutic agents.

Although reports exist on a wide variety of topical hemostatic agents, currently approved agents fall into 4 functional categories: mechanical barrier agents, biologically active agents, flowable sealants (thrombin plus a mechanical barrier agent), and fibrin sealants. These agents differ in mechanism of action, efficacy, safety profile, and type of formulations (Table 1). A brief review of each type of topical hemostasis enhancing agent helps clarify subsequent recommendations for its clinical use (Table 2).
Table 1. Topical Hemostatic Products

<table>
<thead>
<tr>
<th>Level I</th>
<th>Level II</th>
<th>Level III (combination hemostats)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent potency/type and mechanism of action</strong></td>
<td><strong>Thrombin, converts fibrinogen to fibrin activated platelet aggregation</strong></td>
<td><strong>Contact activation + fibrinogen converted to fibrin</strong></td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td><strong>Capillary, oozing arteriolar</strong></td>
<td><strong>Capillary, oozing minor bleeding</strong></td>
</tr>
<tr>
<td><strong>Coagulation status</strong></td>
<td><strong>Intact</strong></td>
<td><strong>Intact through coagulopathic</strong></td>
</tr>
<tr>
<td><strong>Component: products; source; cost</strong></td>
<td><strong>Porcine gelatin:</strong> Gelfoam, Surgifoam; porcine; $4.98−$131</td>
<td><strong>Bovine thrombin:</strong> Thrombin JMI; bovine (5,000 u); $57.23</td>
</tr>
<tr>
<td></td>
<td><strong>Bovine collagen:</strong></td>
<td><strong>Human thrombin:</strong> Evithrom; human (5 mL)</td>
</tr>
<tr>
<td></td>
<td><strong>Avitene; bovine; $90−$167</strong></td>
<td><strong>Recombinant human thrombin:</strong> Recothrom; recombinant (5,000 u)</td>
</tr>
<tr>
<td></td>
<td><strong>Helistar; bovine; $10.12−$155</strong></td>
<td><strong>Vitagel:</strong> recombinant, patients own plasma</td>
</tr>
<tr>
<td></td>
<td><strong>Oxidized regenerated cellulose:</strong> Surgicel; plant; $25−$191</td>
<td><strong>D-Stat:</strong> bovine Thrombi-Gel; bovine; $38−$77</td>
</tr>
<tr>
<td></td>
<td><strong>Surgicel Nu-Kit; plant; $14−$187</strong></td>
<td><strong>Surgiflo:</strong> porcine</td>
</tr>
<tr>
<td></td>
<td><strong>Polysaccharide spheres:</strong> Arista AH, Hemostase MPH, Vitasure; plant; $190</td>
<td><strong>Will depend on size</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Helitene, Instat, Instat MCH; bovine Surgicel fibrillar; plant; $83−$192</strong></td>
<td><strong>Thrombin JMI; bovine (5,000 u); 20% discount, $45.56</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Surgicel SNoW; plant; $84−$192</strong></td>
<td><strong>Evithrom; human (5 mL); 20% discount, $93.60</strong></td>
</tr>
<tr>
<td><strong>Comparative cost</strong></td>
<td><strong>Gelfoam, Surgifoam; $</strong></td>
<td><strong>Thrombin JMI; $</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Avitene, Helitene; $</strong></td>
<td><strong>Evithrom; $</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Surgicel, Surgicel fibrillar; $</strong></td>
<td><strong>Recomthrom; $</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Manufacturers of products listed: Gelfoam (Pfizer); Surgifoam (Ethicon); Avitene (Davol); Helistat/Helitene (Integra Life Science); Instat/Instat MCH (Integra Life Science); Surgicel and Surgicel SNoW (Johnson& Johnson); Arista AH (Medafor); Hemostase MPH (Cryolife Inc.); Vitasure (Medafor); Thrombin JMI (Gen Trac); Evithrom (Ethicon); Recothrom (Zymogenetics); Floseal (Baxter); Vitagel (Stryker); D-Stat (Vascular Solutions); Thrombi-Gel (Vascular Solutions); Surgiflo (Ethicon); Tisseel (Baxter); Evicel (Ethicon); Tachosil (Baxter); Evarrest (Ethicon); Crossel (American Red Cross); Coseal (Baxter); BioGlue (Cryolife Inc.). Product costs are presented as ranges due to the availability of multiple sizes, as cost will depend on the product size chosen.
Mechanical barrier topical hemostatic agents

Mechanical hemostats form physical barriers that block blood flow and create thrombogenic surfaces, allowing blood to clot more rapidly. They achieve hemostasis by using patients’ own circulating coagulation factors. Therefore, they are optimal for patients with an intact coagulation system. Mechanical hemostats are primarily used in cases of minimal bleeding. There are 4 general categories of mechanical hemostats: porcine gelatin, bovine collagen, oxidized regenerated cellulose, and polysaccharide spheres. These agents are low cost, easy to use, and are available in several different forms, including sponges, powders, strips, and sheets. These agents are biodegradable, with decomposition rates ranging from 24 hours (polysaccharide spheres) to 6 weeks (porcine gelatin).

Mechanical barrier hemostatic agents have a relatively complication-free safety profile. Most recognized adverse effects, including swelling, infection, and inflammatory and allergic reactions, are minor and well tolerated. Oxidized regenerated cellulose topical agents reduce infection risk by creating an acidic environment. Expansion and swelling of mechanical hemostats may cause compression of nerves or tissues, especially in closed spaces such as the cranial or spine. For example, gelatin sponge hemostatic agents can expand by up to 200% of their initial volume in vivo. Products of animal origin, such as bovine gelatin and porcine collagen, have an increased risk of infrequent allergic reactions compared with products of human origin. Common applications of mechanical hemostatic agents include use as adjuncts for vascular anastomotic hemostasis and for major liver resections or injuries.

Mechanical hemostatic agents have made their way into the military, emergency medical services, and public domains. Perhaps most notably, procoagulant dressings such as kaolin-based Quik-Clot (Z-Medica), have been embraced as a tier 1 recommendation for battlefield tactical combat casualty care for injured combatants with severe hemorrhage on the basis of the product’s performance in controlling severe extremity hemorrhage. Procoagulant dressings, of which Quik-Clot is but 1 example, come in a variety of shapes and sizes and are suitable for direct application as well as packing into cavities. No special skill is required to apply these dressings, but they are best removed only by medical professionals in a definitive control location due to the risk of recurrent hemorrhage. To wit, these dressings may be purchased as part of a medical emergency kit, as a stand-alone belt kit, and may be accompanied by a tourniquet for severe extremity injury management. Unsurprisingly, mechanical hemostatic dressings are also well used as part of wilderness medicine preparedness. Similarly, such kits are increasingly deployed among special weapons and tactics teams as well as in police patrol unit mobile platforms as context-appropriate replacements for the aging medical kits commonly used by police who serve as first responders. In parallel, procoagulant dressings are also being tracked into emergency departments as well as the operating room. Like many other topical hemostats, these dressings are generally not regulated by the Pharmacy department, but are commonly distributed by Central Supply. Therefore, use of these products within the hospital remains unclear.

Biologically active agents

The thrombin products are biologically active topical hemostatic agents. They are indicated for cases of minor bleeding and oozing from accessible microvasculature. Thrombin-containing topical hemostats promote fibrin clot formation by direct action on fibrinogen. In contrast to the mechanical agents, thrombin-containing topical agents do not rely on patients’ intrinsic clotting mechanism to the same extent as do mechanical hemostatic agents, and can be used in patients with impaired coagulation in the presence of adequate fibrinogen levels. The 3 types of thrombin agents are bovine thrombin, pooled human plasma thrombin, and recombinant thrombin. Studies have shown that all 3 types have comparable efficacy.

Thrombin can be used in a variety of ways: by itself as a drip or a spray, combined with an absorbable hemostat, or in a manufactured fibrinogen-thrombin combination (fibrin sealant). Application of thrombin spray serves as a hemostat for minor bleeding occurring on large raw surfaces such as burns, adhesions, vascular suture lines, organ parenchyma, or muscle bleeding. Gelatin-thrombin combinations applied to bleeding surfaces in vascular and neurosurgical procedures augment hemostasis. Fibrin sealants, a combination of thrombin and a source of fibrinogen, are commonly used for a wide variety of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimal bleeding</th>
<th>Mild bleeding</th>
<th>Moderate bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>Level I (mechanical hemostat)</td>
<td>Level I (mechanical hemostat)</td>
<td>Level III (fibrin sealant, combination hemostat)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Level II (Thrombin)</td>
<td>Level II (Thrombin)</td>
<td>Level III (fibrin sealant, combination hemostat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Level III (fibrin sealant, combination hemostat)</td>
<td></td>
</tr>
</tbody>
</table>
surgical procedures. There are differences in the safety profiles of thrombin-containing topical hemostatic agents related to the source of thrombin (bovine, human, or recombinant). Because of these safety differences, clinicians should be aware of both the source of thrombin and possible thrombin additives in each preparation. There is a risk of immune-mediated coagulopathy on re-exposure to bovine thrombin, presumably related to sensitization to bovine proteins present in the bovine thrombin preparation. For this reason, the bovine thrombin package insert carries an FDA black box warning cautioning against re-exposure. Initial exposure to bovine thrombin may cause development of antibodies to thrombin factor V or other proteins found in these preparations. Secondary exposure can stimulate an immunologic response, impairment of normal hemostasis, and postoperative adverse events, leading to life-threatening bleeding, anaphylactic reactions, or death. Reports suggest that antibody production also occurs in patients treated with pooled human thrombin and recombinant human thrombin, but the incidence and seroconversion rates are much lower than those with bovine thrombin.

Human pooled plasma thrombin carries a theoretic risk of transmitting blood-borne pathogens such as HIV, hepatitis, or prion disease. To date, there have been no documented cases of infection transmission associated with the use of pooled human thrombin. Recombinant human thrombin has neither the risk of antibody development associated with bovine thrombin nor the risk of viral transmission associated with pooled human plasma thrombin. However, there is a theoretic risk of allergic reactions in patients who are allergic to the hamster cell lines or snake proteases used in the manufacture of recombinant human thrombin. Ballard and colleagues compared recombinant thrombin to bovine thrombin, demonstrating comparable efficacy with a similar incidence of adverse events. The development of antiprotein antibodies was significantly greater (p = 0.001) in the bovine thrombin group (21.5%) compared with the recombinant group (1.5%).

Flowable topical hemostatic agents

Flowable hemostatic agents combine thrombin with a mechanical hemostat to form a “flowable” paste-like mixture delivered via a syringe-type applicator. These agents work on actively bleeding tissue and have the advantage of conforming to the shape of irregular wound surfaces. Flowables can be applied either focally or spread to cover larger areas of bleeding from oozing to spurting. These agents combine the mechanisms of action of both agents to mechanically obstruct blood flow and to actively convert patients’ fibrinogen to fibrin at sites of bleeding. They also combine the risks of both mechanical agents and the thrombin product used.

Several randomized controlled trials demonstrated the efficacy of these agents using bovine gelatin matrix and thrombin. A trial of a flowable bovine gelatin matrix—thrombin product compared with porcine gelatin sponge and bovine thrombin—demonstrated superiority in time to hemostasis (p < 0.001) of the flowable product. Analyses of this trial, stratified by operative procedure including vascular and cardiac operations, also showed superiority of the flowable agent. Randomized controlled trials in adenoidectomy and adenotonsillectomy also demonstrated more rapid hemostasis with a bovine gelatin matrix with thrombin. Trials in patients undergoing cardiac surgery and thyroidectomy showed superiority of the flowable bovine gelatin matrix-thrombin product compared with oxidized cellulose mechanical topical hemostats.

Topical fibrin sealants

Fibrin sealants are dual-component products that combine high concentrations of human fibrinogen with human, bovine, or recombinant thrombin immediately before use. Some products also contain aprotinin and an antifibrinolytic agent to ensure maintenance of stable fibrin clots. Calcium chloride, a coagulation protein cofactor, is also found in some products. Fibrin sealants cause faster clot formation than patients’ own coagulation processes, and provide fibrinogen concentrations 15 to 25 times greater than the physiologic concentrations at sites of bleeding. Fibrin sealants exert their effects at the end of the coagulation cascade, where fibrinogen is converted to fibrin in the presence of thrombin and calcium. Thrombin also activates factor XII to stabilize clot. A fibrin sealant forms both a hemostatic plug and a matrix to enhance wound healing. Because this process is independent of earlier steps in the coagulation cascade, fibrin sealants remain effective in patients with defects in other parts of their coagulation pathways. Fibrin sealants may be applied to tiny blood vessels and to places that cannot be reached by conventional sutures. A comparison of fibrin sealant with other hemostatic agents in cardiac surgery and emergency sternotomy patients showed faster bleeding control and decreased postoperative blood loss in patients treated with fibrin sealant. Several randomized, controlled trials demonstrated the efficacy of fibrin sealants in cardiac, vascular, and major abdominal procedures. Fibrin sealant products are available in liquid form, and as part of absorbable patches. The safety profile of these agents includes the theoretic infectious risk of pooled plasma derivatives and anaphylactic reactions to aprotinin. Additional safety issues include application of overly thick layers, leading to
infection and poor healing, and air emboli from sprayers used for liquid fibrin sealant application.

**Product use**

It is clear that product design affects the niche that each product will occupy with regard to hemorrhage control in the operating room. For example, a flowable topical hemostat would not be suitable for active hemorrhaging; instead a procoagulant impregnated sponge might be the preferred choice. A variety of factors, including surgeon’s preference, previous experience with a particular agent, rapidity of deployment, and product availability (frequently without regard to cost) appear to guide surgeons’ choices of topical hemostats, rather than specific knowledge of the characteristics of each agent. Predictably, there is widespread practice variation in the clinical use of topical hemostatic agents.

There is no direction for the clinician on which product type is best for a given clinical situation, and in most cases, use of these agents is not based on evidence or clinical practice guidelines. In 2006, the American Society of Anesthesiologists (ASA) published “Practice Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies.”61 The only mention of topical hemostatic agents in this document suggests that, “Topical hemostatics (eg, fibrin glue or thrombin gel) should be administered for the control of excessive bleeding.”

In 2011, the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists (STS/SCA) released updated guidelines on perioperative blood transfusion and blood conservation in cardiac surgery7 that include an assessment of topical hemostatic agents. Their recommendation states, “Topical hemostatic agents that employ localized compression or provide wound sealing may be considered to provide local hemostasis at anastomotic sites as part of a multi-modality blood management program. (Class IIb, Level C)”76 However, the panel also recognized that although topical hemostats are commonly used in cardiac surgery, there is currently no agent of choice.

Unlike other circumstances in which there are a plethora of evidence-based recommendations and guidelines, the use of topical hemostatic agents in the operating room principally reflects local practice and physician preference. Moreover, the true scope of practice is likely unclear because topical hemostats may be stocked in multiple locations including the operating room, central supply, pharmacy, or the blood bank depending on local practice and product type. Therefore, obtaining a reliable evaluation of current practice to glean data from which to make evidence-based recommendations is a significant challenge.

There are a number of comprehensive reviews that provide an overview of available hemostatic agents and attempt to categorize these agents in various ways.31,32,62-67 The majority of these classifications follow a product-based approach, classifying agents based on their mechanism of action, pharmacology, or product characteristics. This characterization works well for manufacturer, wholesaler, and inventory stocking, but is not well suited to clinical practice (Table 1).31,32,63,65-67 Categorizing products in a functional fashion, as has been done here (Tables 1 and 2), may better enable clinicians to match a particular class of product to a specific clinical circumstance.

**Clinical factors**

Coagulation status, severity and type of bleeding, hemorrhage site and accessibility, and type of surgical procedure are all factors that deserve consideration when managing perioperative bleeding.68 Recognizing that hemorrhage control is a time-sensitive activity, a rapid decision pathway would be a useful aid for clinicians in the selection of an optimal agent for particular characteristics of bleeding in vivo. Accordingly, this panel has developed an algorithm for when to use topical hemostatic agents and a table whose initial major branch point is hemorrhage severity (Fig. 1, Table 2). It is intuitively obvious, but cannot be overstated, that the optimal agent for localized microvascular hemorrhage may be quite different from that for diffuse microvascular hemorrhage or venous oozing from raw surfaces after major organ resection (eg, partial hepatectomy).

**Product addition, tracking, and clinical guidelines**

The process to add topical hemostatic agents to a hospital formulary is often quite distinct from that for new medications or component blood products. The former often bypasses the Pharmacy and Therapeutics Committee; the latter requires committee review and formal approval. Additionally, topical hemostats can be either biologic products or implants. Many products are temporarily deployed and removed after clotting has occurred, or are diffuse (as in the flowable products) and cannot be specifically localized after use.

Optimal formulary management of topical hemostatic agents requires multidisciplinary collaboration between surgeons, anesthesiologists, nurses, pharmacists, and other health care professionals. Such collaborations may evaluate clinical need, current use, product efficacy, and cost in a fashion that supports favorable outcomes and optimizes resource use. Formulary inclusion of multiple agents with the same form and mechanism of action is both redundant and wasteful. Institutional guidelines are needed in order to guide the optimal, safe, and cost-effective use of these agents.
Product tracking of topical hemostatic agents supports the Joint Commission’s National Patient Safety Goals, requiring accurate and complete reconciliation of all medications across the continuum of care. The practical application of this patient safety initiative is that all medications should be listed in patients’ medical records, including topical hemostatic agents. Because many topical hemostatic agents are drugs, or contain a drug component, addressing this Joint Commissions mandate involves a practice change in nearly every instance of topical hemostatic use. A prime example of the need for trackable reporting of hemostasis-enhancing agents is that of previous bovine thrombin exposure, the most common causal factor in development of immune-mediated coagulopathy. Antigen exposure (previous bovine thrombin administration) is rarely documented in the medical record. More than 60 cases with known or presumed surgical exposure to bovine thrombin have been published. Bleeding was noted in approximately one-half of these cases. However, documentation of such exposure is not routinely available in patient medical records. Identifying patients with previous exposure is necessary to assess risk of planned or unplanned re-exposure with thrombin-containing agents. Continued failure to treat topical agents as drugs and/or devices exacerbates the risk of bovine thrombin-related coagulopathy, and potentially other untoward outcomes. The lack of documentation of use of these agents is a deficit in patient care with significant safety implications.

Furthermore, there is a need for patient advocacy and cultural sensitivity in considering use of topical hemostatic agents, just as there is in the use of blood transfusions. For
some patient populations, blood product administration is not an option for religious or other reasons. Because different topical products contain blood-derived agents, administration of these agents may infringe on patient autonomy and patient rights. Receiving these products without consent raises potentially avoidable ethical and legal issues. Preplanned approaches to topical hemostat use in specific patient populations can help avoid these issues. It is virtually unheard of for patients to sign a consent form that addresses the use of topical hemostatic agents. Because surgeons may not even be aware of the presence of human- or animal-derived proteins in the products they use, an algorithm that is sensitive to product contents can obviate this potential pitfall.

**Efficacy**

As the panel’s review discovered, there are limited data regarding the comparative efficacy of topical hemostatic agents in clinical practice. There are no reliable guidelines about when hemostatic agents are best used or which products are optimal for specific procedures. Information on the impact of these agents on clinical outcomes, including overall blood loss and transfusion rates, is lacking. Without benchmark data, determination of best practice and quality improvement initiatives is difficult. Most of these products shorten bleeding times in both animal and human studies, but the metric used to assess efficacy may not be clinically relevant. Finally, there is little information linking the use of these products to improved patient outcomes. Clearly more research in this area is needed.

In the absence of an ideal measure of efficacy for topical hemostatic agents, regulatory organizations, including the FDA, use attainment of hemostasis within 10 minutes of application as their standard for product approval. The advent of newer and more accurate measures of coagulation and of blood loss may create new metrics for evaluating these preparations. Clinically meaningful outcomes measures could include operating room time, transfusion rates, and overall cost of care for surgical admissions. The most useful measures have yet to be determined.

**Cell recovery**

The use of topical hemostatic agents with cell recovery remains controversial. Both the manufacturer of the Cell Saver (Haemonetics) and the American Association of Blood Banks have recommended against the use of the Cell Saver in conjunction with procoagulant agents, including fibrin glue, microfibrillar collagen, and thrombin, as these agents may cause blood in intraoperative salvage reservoirs to clot. In 2009 the FDA received 3 reports of pulmonary embolism related to spine procedures performed with the concomitant use of blood recovery system and topical hemostatic agents. In each of these cases, the pulmonary embolism occurred after reinfusion of recovered blood. However, other reports document the apparent safe and successful use of the combination of topical hemostatic agents and properly washed cell recovery. Therefore, there appears to be no contraindication to the careful use of topical hemostatic agents with a cell recovery device, providing the amount of the agent suctioned from the wound into the collection reservoir is minimal. One technique that may be used to accomplish this is to discontinue the use of blood salvaging suction tips immediately before use of topical hemostatic.

**Transfusion avoidance**

In addition to common sense that reduced intraoperative hemorrhage decreases the intraoperative transfusion rate, there is evidence to support this contention. Eleven clinical trials showed a decreased transfusion rate with the use of topical hemostats; 11 others, with dissimilar structure, showed no difference with regard to transfusion. The impact of topical hemostat use on transfusion depends on the type of operation. Comparative

---

**Table 3. Recommendations**

1. Hospital leaders need to become aware of the topical hemostatic agents used in their institutions and determine the circumstances of their use.
2. Many topical hemostatic products are drugs or have a drug component and should be treated as such. Medication products are to be stored, handled, and processed within institution-specific policies and should be subject to formulary review.
3. The use of topical hemostatic agents needs to be recorded in a manner that is practical, searchable, and easily retrievable.
4. Patient and clinician education initiatives are needed to improve knowledge of these products, their origins, their safety profiles, and their place in therapy.
5. Industry and investigators need to determine clinically relevant study endpoints. The current gold standard of “hemostasis at 10 minutes” may be too long for clinical relevance. New, clinically relevant ways to determine clinical impact of topical hemostatic agents on bleeding need to be developed and implemented (procedure time, anesthetic exposure, readmission rate, length of stay, infection).
6. There is a need for more “head-to-head” studies to identify which products are better for specific clinical situations.
7. Safety and use data should be recorded at the patient and provider level in order to identify patterns of use and determine best practices.

Data collection should be stratified by patient, procedure, provider, clinical service or department, hospital-wide and across hospitals.
trials used lax transfusion guidelines and did not use transfusion rate as a primary outcome. Robust, well-designed studies to determine the effect of topical hemostatic agents on transfusion rates are needed.

CONCLUSIONS
The use of topical hemostatic agents in the operating room is very common. Because these hemostatic products tend to bypass the formulary approval process, there is currently no systematic approach to acquisition and documentation of use of these agents in the hospital. In addition, their place in clinical practice is not always evidence-based, and they are not systematically evaluated and managed in many institutions. Furthermore, the plethora of available agents establishes duplicative products within the same class and that use the same mechanism of action, leading to a bewildering array of choices for clinicians. This panel has presented recommendations aimed toward alleviating this problem (Table 3), and it also provides a rubric for use triggered by the magnitude of hemorrhage that is encountered and further refined by clinical circumstance. Such an approach may help clinicians make rapid decisions about adjunctive hemostasis when encountering hemorrhage in the operating room. Careful inquiry into the impact of the use of topical hemostatic agents on component therapy and clinical outcomes may further delineate optimal use of these widely available procoagulant agents.

Author Contributions
Study conception and design: Shander, Kaplan, Harris, Gross, Nagarsheth, Nemeth, Ozawa, Riley, Ashton, Ferraris
Acquisition of data: Shander, Kaplan, Harris, Gross, Nagarsheth, Nemeth, Ozawa, Riley, Ashton, Ferraris
Analysis and interpretation of data: Shander, Kaplan, Harris, Gross, Nagarsheth, Nemeth, Ozawa, Riley, Ashton, Ferraris
Drafting of manuscript: Shander, Ashton, Ferraris
Critical revision: Shander, Kaplan, Harris, Gross, Nagarsheth, Nemeth, Ozawa, Riley, Ashton, Ferraris

REFERENCES
20. Vitagel [instructions for use], Malvern, PA: Stryker; P/N 5332–0002.


APPENDIX 1. SUPPLEMENTAL INFORMATION METHODS

The panel approached their task in 3 phases: in-depth literature search and review, face-to-face group discussion with adjunctive literature search and review, and iterative manuscript generation. The panel opted to use available data to craft recommendations using previously published reviews and other recently published material.1-6 The paucity of high quality published comparative trials precluded the use of rigid consensus methodology such as a modified Delphi Appropriate Consensus approach.

The initial literature search (MEDLINE and PubMed) used the following keywords: topical hemostatics, hemostasis AND Gelfoam, Surgicel, Floseal, D-Stat, Vitagel, Thrombin, Recothrom, Ethithrom, Tisseal, Evisel, Tachosil, Coseal, BioGlue. The search was limited to randomized clinical trials, clinical trials, systematic reviews, and meta-analyses. The panel collected important features of each reviewed article including the agent used, any comparator, operative procedure used, primary outcomes measure(s), transfusion exposure, and adverse events. Types of studies excluded from review by the authors are listed in Supplemental Table 1.

RESULTS

The initial literature search identified 267 manuscripts. Using the inclusion criteria described above, 76 articles were found to be suitable for further review (Appendix 2). Fifty-nine of these demonstrated efficacy of a topical hemostatic agent.Evaluated comparators included: no agent (30 reports),1,2,14-25,31,36,38,54,56,58,60-63,68,69,72,74,76,78,80,81 mechanical (barrier) topical hemostatic agent (16 reports),1,11,14-16,19,36,37,39,43,44,50-52,72 another topical hemostatic agent (12 reports),7,13,14,23,25,30,32,35,48,54,73,78,80 and nonpharmacologic hemostat (9 reports).3,4,10,20,22,27,28,33,46,57 Eight trials1,3,15,30,35,37,75,77,79 found no benefit against the comparator agent, but 3 of these compared bovine to recombinant thrombin and 1 compared 2 formulations of the same agent.30 The most common primary outcomes measure was attainment of hemostasis within 10 minutes (the current standard clinical research endpoint) of application of test agent. Nine trials1,7,9,15,30,35,37,75,77,79 encompassed safety analyses and did not evaluate efficacy.

REFERENCES


**Supplemental Table 1.** Studies Excluded from Review

<table>
<thead>
<tr>
<th>Excluded studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal studies</td>
</tr>
<tr>
<td>Non-FDA approved product reports</td>
</tr>
<tr>
<td>Non-English language manuscripts</td>
</tr>
<tr>
<td>Reports of autologous hemostatic products</td>
</tr>
<tr>
<td>Products used as tissue or blood vessel sealants and adhesives but labeled for non-hemostatic indications (e.g., pulmonary parenchymal leaks)</td>
</tr>
<tr>
<td>Case reports with limited applicability</td>
</tr>
</tbody>
</table>

**Supplemental Figure 1.** Literature search results.