Local/topical hemostatic agents for treatment of postpartum hemorrhage

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
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Statement of need

Obstetric hemorrhage is estimated to cause 25 percent of all maternal deaths and is the leading direct cause of maternal mortality worldwide.¹ Immediate postpartum hemorrhage (PPH), defined as vaginal bleeding in excess of 500 mL in the first 24 hours after delivery, accounts for most cases of obstetric hemorrhage, occurs in over 10 percent of all births, and is associated with a 1 percent case-fatality rate.² Additionally, if women do survive PPH, approximately 12 percent will have severe anemia.³ Also, if women survive severe PPH (greater than 1,000 mL of blood loss) (“near misses”), they are significantly more likely to die in the year following the PPH.⁴ The United Nations Millennium Development Goal 5, to reduce 75 percent of maternal mortality by 2015, cannot be reached without significant improvements in PPH-related mortality.⁵,⁶

There are four specific causes of immediate PPH that can be remembered with the well-known mnemonic of the “Four Ts”:⁷

- **Tone:** Uterine atony, or inadequate uterine contraction, is the most common cause of severe PPH in the first 24 hours after childbirth. Contractions of the uterine muscle fibers help to compress maternal blood vessels. Bleeding may continue from the placental site if contractions are inadequate. Clinically, 70 to 90 percent of all immediate PPH is due to uterine atony.

- **Trauma:** Lacerations, hematomas, uterine inversion, and uterine rupture are responsible for up to 20 percent of PPH. In countries where non-specialist physicians perform cesarean operations, “trauma” caused by complications of cesareans may become increasingly common. For example, a confidential enquiry into maternal deaths in South Africa for the period 2008–2010 found that bleeding during and after cesarean accounted for 26.2 percent of deaths due to obstetric hemorrhage.⁸

- **Tissue:** Retained placenta or placental fragments, or invasive placenta (accreta/increta/percreta) are responsible for up to 10 percent of PPH. The rising cesarean birth rate may result in an increase in the proportion of PPH caused by placenta praevia and placenta accreta, as they are associated with cesarean operations.⁹

- **Thrombin:** Although uncommon, clotting disorders are responsible for approximately 1 percent of PPH cases. Coagulation defects may be acquired or congenital and may be associated with thrombocytopenia and/or hemostatic defects. Acquired causes include disorders that are related to conditions of pregnancy (e.g., severe preeclampsia, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, abruptio placentae, fetal demise, amniotic fluid embolism, massive hemorrhage, and sepsis), surgical site bleeding, or medications.

Outcomes from PPH depend on the timeliness of the response. When births occur in the home, outcomes depend on initiating first aid as temporizing measures until definitive management can be provided. When women have access to skilled birth attendants or surgery, access to conservative adjunct interventions to control bleeding may be lifesaving and could prevent radical surgery when standard techniques (such as uterotonic drugs, suturing, ligature, cautery, or pressure) are insufficient or impractical to implement.
Local (also known as “topical”) hemostatic agents (LHAs) are applied directly to the affected area of the body and can be used either as a “first aid” measure or as adjunct therapy for management of PPH. They have potential for use at all points of care because they do not require injection, many do not require storage in the cold chain, they have fewer adverse effects than systemic hemostatic agents, and their application is relatively simple. An additional advantage is that LHAs have the potential to be used to manage bleeding due to multiple causes: tone (bleeding at the placental implantation site due to uterine atony), trauma (lacerations, bleeding at surgical incision sites, bleeding in hard to reach areas), or thrombin (coagulopathies). While some novel technologies apply LHAs to gloves or gauze used to manually remove a placenta (tissue), the LHAs induce hemostasis at the placental implantation site after the placenta has been safely removed.

Factors affecting the selection of an appropriate LHA include potential use, severity of bleeding, site (internal or external), cause of bleeding (lacerations, vascular, arterial, coagulopathy), and the personal experience and preference of the provider. These are important and will affect the clinical outcome for the patient. Use of LHAs for PPH in low-resource settings (LRS) will depend on these factors as well as considerations of ease of use, cost, and storage requirements. Ideal qualities of LHAs for PPH use include: 

- Ability to rapidly promote hemostasis and control bleeding.
- Safe to use with no risk of injury to tissues or transmission of infection.
- Affordability.
- Safety.
- Stability at room temperature (RT).
- No or minimal requirements for mixing or pre-application preparation.
- Simplicity of handling and application.
- Availability in multiple forms for versatility.

**Technology solutions landscape**

The US Food and Drug Administration (FDA) approved the introduction of the first widely accepted tissue glue in 1998, and LHAs have been used successfully in neurosurgery, urology, orthopedics, trauma medicine, and gynecology. LHAs come in a range of configurations (see Appendix A for an overview of available LHAs):

- **Mechanical agents:** These agents produce swelling and cause a mechanical barrier to bleeding and oozing. They require an intact coagulation system. They can be used with saline or thrombin.

* Please note that this landscape only focuses on local (applied directly to the bleeding site) hemostatic agents and does not address use of systemic (administered parenterally) hemostatic agents.
• **Biologically active agents:** These are thrombin-containing products that require intact fibrinogen and do not rely on the patient’s intrinsic clotting system. Thrombin converts fibrinogen to fibrin, stimulating activity in the coagulation cascade.

• **Flowable agents:** These LHAs have a thick, flowable consistency and combine both active (thrombin) and mechanical hemostatic agents (collagen or gelatin).

• **Topical fibrin sealants:** These LHAs combine high concentrations of human fibrinogen and thrombin. May also contain antifibrinolytic (e.g., aprotinin) to stabilize the clot.

• **Antifibrinolytic agents:** These agents prevent clot breakdown (fibrinolysis) in order to reduce surgical blood loss.

• **Nonfibrin sealants and tissue adhesives:** Tissue adhesives can be used to promote hemostasis, but are predominantly used as an alternative to sutures for tissue approximation.

• **Novel LHAs:** Several upstream LHAs are available that work primarily by exerting physical effects or by enhancing existing hemostatic mechanisms.

Unfortunately high-quality data establishing the effectiveness of LHAs are lacking. There are some published randomized controlled trials (RCTs) in which LHAs were used for minor intraoperative bleeding sites, including (but not limited to):

• Comparison of hemostatic sealants (Floseal®, Proceed™ [Baxter Healthcare],) and thrombin-gelatin combination (Gelfoam® [Pharmacia & UpJohn]-thrombin): In three trials, hemostatic sealants were found to have significantly higher rates of hemostasis (88 to 99 versus 57 to 93 percent) at ten minutes after application compared with thrombin-gelatin combination in cases involving patients undergoing vascular, spinal, or cardiac surgery.\(^\text{16-18}\)

• Comparison of autologous fibrin sealant (Vivostat® [Vivostat A/S]-derived sealant) and oxidized regenerated cellulose (Surgicel® [Ethicon]): In a prospective, randomized, multicenter clinical study, use of an autologous fibrin sealant resulted in a significantly higher rate of hemostasis (94 versus 65 percent) at five minutes after application in 69 patients undergoing obstetric, gynecologic, general, vascular, and cardiothoracic surgery.\(^\text{19}\)

• Comparison of fibrin sealant and a conventional LHA: In a multicenter trial, 333 patients were randomly assigned to receive the fibrin sealant or a conventional topical hemostatic agent in patients undergoing either reoperative cardiac surgery (redo) or emergency resternotomy.\(^\text{20}\) Fibrin sealant controlled bleeding successfully within five minutes of application in significantly more patients (93 versus 12 percent) compared with conventional LHAs.

To date, there have been no published reports on RCTs on use of LHAs in cases of PPH occurring in LRS. There is an ongoing clinical trial\(^\text{21}\) to assess the safety and efficacy of HemCon GuardaCare®XR (HemCon Medical Technologies [chitosan technology]) compared to standard bandaging in subjects with PPH as a result of cervical and vaginal lacerations; as of April 2014, the study was still open and had no published reports. However, there is now growing evidence, in the form of published case studies, to
support their use for PPH management in cases of uterine atony, placenta praevia, vaginal lacerations, hemorrhage at the uterine incision site, arterial and venous bleeding, placenta accreta/increta/percreta, or anticoagulation (see Appendix B). All of the configurations described above—except for biologically active, topical use of antifibrinolytic agents, and nonfibrin sealants and tissue adhesives—have published case studies about their use for PPH (see Table 1).

In addition to LHAs listed in Table 1, topical application of antifibrinolytic agents (most notably tranexamic acid [TXA]), nonfibrin sealants/tissue adhesives, and biologically active LHAs are also potential candidates for use for PPH in LRS, although there are no published case studies of their use in PPH management (see Table 2).
### Table 1. Local hemostatic agents used successfully for management of postpartum hemorrhage.

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanical agents</th>
<th>Flowable agent</th>
<th>Topical fibrin sealants</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chitosan-covered gauze</td>
<td>Porcine gelatin sponge</td>
<td>Gelatin-thrombin matrix</td>
<td>Human fibrinogen and thrombin</td>
</tr>
<tr>
<td></td>
<td>Kaolin-infused gauzes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>QuikClot® (Z-Medica)</td>
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<tr>
<td></td>
<td>Gelatin-thrombin matrix</td>
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<tr>
<td></td>
<td>Floseal® (Baxter Healthcare)</td>
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<td></td>
<td>TachoSil® (Nycomed Pharma)</td>
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<tr>
<td></td>
<td>TISSEEL® (Baxter Healthcare)</td>
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<td>ABS® (Ankaferd Health Products)</td>
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<td>Product names</td>
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<td></td>
<td>• Arsenal foam</td>
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<td></td>
<td>• XStat™ (RevMedx)</td>
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<td>• Celox™ (Medtrade)</td>
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<tr>
<td></td>
<td>• QuikClot® (Z-Medica)</td>
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</tr>
<tr>
<td></td>
<td>• Gelfoam® (Pharmacia &amp; UpJohn)</td>
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<tr>
<td></td>
<td>• Floseal® (Baxter Healthcare)</td>
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<tr>
<td></td>
<td>• TachoSil® (Nycomed Pharma)</td>
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<tr>
<td></td>
<td>• TISSEEL® (Baxter Healthcare)</td>
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<td></td>
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<tr>
<td></td>
<td>• ABS® (Ankaferd Health Products)</td>
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<tr>
<td></td>
<td>Case studies of successful use for postpartum hemorrhage</td>
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<tr>
<td></td>
<td>Tone</td>
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<tr>
<td></td>
<td>• Uterine atony.</td>
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<tr>
<td></td>
<td>• Bleeding at placental implantation site.</td>
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</tr>
<tr>
<td></td>
<td>• During uterine arterial embolization for uterine atony.18</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>• Uterine atony.</td>
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<tr>
<td></td>
<td>• Bleeding at placental implantation site.</td>
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<tr>
<td></td>
<td>• Intractable lower uterine segment hemorrhage.</td>
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<tr>
<td></td>
<td>Trauma</td>
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<tr>
<td></td>
<td>• Hemorrhage at the uterine incision site.</td>
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<tr>
<td></td>
<td>• Bleeding from multiple vaginal lacerations.</td>
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<tr>
<td></td>
<td>• Complicated obstetric lacerations.</td>
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<tr>
<td></td>
<td>Thrombin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Coagulopathy</td>
<td></td>
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<tr>
<td></td>
<td>Ability to rapidly promote hemostasis and control bleeding</td>
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<tr>
<td></td>
<td>Hemostasis typically achieved in 3 to 5 minutes.</td>
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<tr>
<td></td>
<td>Hemostasis typically achieved in 2 to 10 minutes.</td>
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</tr>
<tr>
<td></td>
<td>Hemostasis typically achieved in 3 to 5 minutes.</td>
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</tr>
<tr>
<td></td>
<td>Hemostasis typically achieved between 30 seconds and 2 minutes.</td>
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<tr>
<td></td>
<td>Affordable</td>
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<td></td>
<td>Least expensive.</td>
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<tr>
<td></td>
<td>More expensive than mechanical.</td>
<td></td>
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<tr>
<td></td>
<td>More expensive than mechanical or flowable.</td>
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<tr>
<td></td>
<td>Stability at room temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stored at room temperature (RT) or “non-extreme” temperatures (&lt;5°C and &gt;60°C).</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Stored at controlled RT (2°C–25°C) or RT.</td>
<td></td>
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<tr>
<td></td>
<td>• Freeze dried: stored at 2°C–25°C.</td>
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<tr>
<td></td>
<td>• Frozen: stored at ≤20°C; thaw 5–10 minutes.</td>
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<td></td>
</tr>
</tbody>
</table>

* Ankaferd blood stopper.
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanical agents</th>
<th>Flowable agent</th>
<th>Topical fibrin sealants</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chitosan-covered gauze</td>
<td>Porcine gelatin sponge</td>
<td>Human fibrinogen and thrombin</td>
<td>Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum, and Urtica dioica</td>
</tr>
</tbody>
</table>
| Safe to use with no risk of injury to tissues or transmission of infection | Risks:  
  • Swelling  
  • Infection | Risks:  
  • Fever  
  • Encapsulation | Risks:  
  • Swelling  
  • Viral/prion disease transmission.  
  • Risks associated with particular standalone thrombin that is chosen. | Risks:  
  • Viral/prion disease transmission.  
  • Antibody formation.  
  • Swelling.  
  • May require intact coagulation.  
  • Air/gas embolism if administered using pressurized gas.  
  • TISSEEL® contains aprotinin (associated with anaphylactic reactions). |
| No or minimal requirements for mixing or pre-application preparation |       | Requires mixing products.       | Patch and sponge are immediately available for use.  
  • Freeze-dried products require warming and mixing products. |       |
| Simplicity of handling and application                              | Relatively easy.                   | Relatively easy.               | Relatively more complex.                       | Relatively easy.                        |
| Availability in multiple forms for versatility                      | Powder  
  • Compression pads  
  • Lyophilized/absorbable sponges  
  • Sprayable liquid  
  • Gelatin powder or paste | Powder  
  • Sponges | Prefilled syringe  
  • TachoSil®: sponges, patches.  
  • TISSEEL®: spray, prefilled syringe. | Spray  
  • Pad/tampon  
  • Sponge |
Table 2. Promising local hemostatic agents for management of postpartum hemorrhage.

<table>
<thead>
<tr>
<th>Class/Type of agent</th>
<th>Antifibrinolytic</th>
<th>Nonfibrin sealant/tissue adhesive</th>
<th>Biologically active agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical TXA²</td>
<td>Nonfibrin sealant/tissue adhesive</td>
<td>• Thrombin, topical (bovine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Thrombin, topical (human)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Thrombin, topical (recombinant)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case studies of successful use for postpartum hemorrhage</th>
<th>No case studies for management of postpartum hemorrhage available.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Ability to rapidly promote hemostasis and control bleeding</th>
<th>Hemostasis typically achieved in 3–5 minutes.</th>
<th>Hemostasis typically achieved in less than 10 minutes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe to use with no risk of injury to tissues or transmission of infection</td>
<td>• Thromboembolic effect uncertain but must be considered.</td>
<td>• Labeling for topical thrombin specifically states that it is not for use in cases of infection or for postpartum hemorrhage or menorrhagia.</td>
</tr>
<tr>
<td></td>
<td>• Inflammatory effects on skin.</td>
<td>• Bovine has received the strongest possible FDA label warning, and can cause fatal severe bleeding or thrombosis.</td>
</tr>
<tr>
<td></td>
<td>• Some sealants must not be used internally; need area to be kept dry for healing to occur.</td>
<td>• Human has risks for plasma-derived infectious disease or anaphylactic or severe systemic reaction to human blood products.</td>
</tr>
<tr>
<td></td>
<td>• Excessive heat generation can occur during polymerization.</td>
<td>• Recombinant has risks of hypersensitivity to hamster or snake proteins.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Affordable</th>
<th>Similar price range to mechanical agents.</th>
<th>More expensive than mechanical agents.</th>
<th>More expensive than mechanical; less expensive than flowable or fibrin sealant.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Stability at room temperature</th>
<th>Should be stored at room temperature (RT) away from direct heat and light.</th>
<th>Stored at controlled RT (5°C–25°C).</th>
<th>Frozen or stored unopened at controlled RT (5°C–25°C).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stable for up to 12 weeks at temperatures up to 50°C.</td>
<td>Store away from moisture, direct heat, and direct light.</td>
<td>Stored at controlled RT (5°C–25°C) or 2°C–8°C after reconstitution.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No or minimal requirements for mixing or pre-application preparation</th>
<th>Relatively easy.</th>
<th>No preparation.</th>
<th>Some are available in prefilled syringes.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Requires mixing with saline.</td>
<td>Adhesiveness makes application relatively difficult.</td>
<td>Others require reconstitution or assemblage of kits.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Simplicity of handling and application</th>
<th>Relatively easy.</th>
<th>Adhesiveness makes application relatively difficult to handle.</th>
<th>Relatively easy.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Availability in multiple forms for versatility</th>
<th>Gel</th>
<th>Spray</th>
<th>Prefilled syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spray kit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pump spray kit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vials</td>
</tr>
<tr>
<td>Class/Type of agent</td>
<td>Antifibrinolytic</td>
<td>Nonfibrin sealant/tissue adhesive</td>
<td>Biologically active agents</td>
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<tr>
<td>--------------------</td>
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<td>---------------------------</td>
</tr>
<tr>
<td>Topical TXA(\text{a})</td>
<td>Nonfibrin sealant/tissue adhesive</td>
<td>• Thrombin, topical (bovine) • Thrombin, topical (human) • Thrombin, topical (recombinant)</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{a}\) Tranexamic acid.
\(\text{b}\) US Food and Drug Administration
Mechanical agents

Mechanical LHAs are applied to a bleeding site using direct pressure and are thought to be most effective when there is minimal bleeding. There are four main categories of mechanical agents: porcine gelatin, bovine collagen, oxidized cellulose, and polysaccharide spheres. They come in various forms: powder, compression pads, lyophilized sponges, absorbable sponges, sprayable liquid, and gelatin powder or paste. Mechanical LHAs can be used to control PPH after both vaginal and cesarean births.

Mechanical LHAs are generally low-cost, easy to use, biodegradable, and immediately available for use (i.e., can be used immediately out of the package). Bovine collagen, porcine gelatin, and oxidized regenerated cellulose may be stored at RT; polysaccharide spheres require storage in “non-extreme” temperatures (<5°C and >60°C). Of the four types of mechanical agents available, bovine and polysaccharide spheres are considered the most effective.

Many of the mechanical agents use animal products, and their potential for causing allergic reactions is of concern. Typically these agents act by expanding quite rapidly, which might compress and cause nerve damage in an enclosed space, such as the uterus or the genital tract. Other potential adverse effects reported have been granulomas at the bleeding sites, abscess formation, and neurological complications.

The following mechanical LHAs have been used to control bleeding due to various causes of PPH:

- Chitosan-coated gauze (Arsenal foam, XStat™ [RevMedx], Celox™ [Medtrade]): uterine atony, placenta accreta/increta, anticoagulation.
- Kaolin-infused gauzes (QuikClot® [Z-Medica]): bleeding from the placental implantation site.
- Porcine gelatin sponge (Gelfoam®): anticoagulation.
- Smectite-impregnated gauze or patches are currently being studied for use in PPH; their use for obstetrics remains in the research phase.

The cost of these mechanical agents ranges from US$5 to US$200 per application. For example, one packet of QuikClot® costs up to US$46 and a packet of Gelfoam® that includes two sterile packs of two sponges each can cost up to US$90. Mechanical products are generally the least-expensive LHAs.

Biologically active agents

There are three origins of topical thrombins: bovine, pooled human plasma, and recombinant. They are used in drip or spray format and are applied with a syringe (when the bleeding may be difficult to reach) or sprayed. Topical thrombins will not work unless bleeding is present. Little is known about the use of these agents for the management of PPH, and no case studies have been reported of use of biologically active agents to manage PPH.

The storage and preparation of biologically active agents depends on the formulation. In general, biologically active agents will need to be refrigerated, and some formulations require storage in a freezer.
Most of the formulations require some kind of reconstitution. All types of thrombins are equally effective at controlling bleeding.

The major concerns with biologically active agents are the possible risks of blood-borne pathogen transmission in pooled plasma thrombin: hypersensitivity to bovine, snake, or hamster thrombin; anaphylactic or severe systemic reaction to human thrombin; antibody formation; and immune coagulopathy.

The cost of these agents ranges from US$50 to US$150 per application. In general, biologically active agents are only slightly more expensive than mechanical agents.

Flowable agents

The combination of active (thrombin) and mechanical hemostatic agents (collagen or gelatin) forms a flowable paste that is used to control bleeding mechanically and by the conversion of fibrinogen to fibrin. Most commonly, these flowable agents are injected by syringe into the bleeding site. The agent then conforms to the shape of the area.

Flowable agents combine the strengths of both mechanical and biologically active LHAs, and consequently have the advantages and disadvantages of both. Flowable LHAs have the same risks/precautions as mechanical and biologically active agents: swelling and viral/prion disease transmission. In addition, particular risks will be associated with the thrombin that is chosen.

Porcine gelatin agents, with or without thrombin, should be stored at controlled RT (2°C to 25°C); bovine gelatin with pooled human thrombin may be stored at RT. All flowable agents require preparation before application, but the ease of preparation varies from one product to another.

Gelatin-thrombin matrix (Floseal®) is a flowable LHA that has been used to control bleeding due to various causes of PPH: atony of the lower uterine segment, bleeding from the placental implantation site, uterine atony associated with disseminated intravascular coagulopathy, bleeding from vaginal cuff and pelvic raw surfaces associated with coagulopathy of sepsis, or scattered arterial and venous bleeding sites that were diffusely distributed over the length of the rectovaginal septum.

The price for flowable hemostatic agents ranges from US$50 to US$250, slightly higher than mechanical and biologically active LHAs.

Topical fibrin sealants

These LHAs 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. Some preparations include an antifibrinolytic agent to prevent lysis of the clot. Fibrin sealants are effective for managing both localized and diffuse bleeding and can be used in patients with coagulopathy who do not have sufficient fibrinogen to form a clot. However, use of this product may require intact coagulation. These LHAs have the greatest amount of trial data available. Comparative trials suggest that topical fibrin sealants are superior to other LHAs.
All formulations of topical fibrin sealants require either freezing or refrigeration. Most products contain two components that require a complex process for coordinating their reconstitution and preparation. In addition, providers must wait at least 15 minutes for frozen components to thaw. A ready-to-use, absorbable patch was FDA approved for cardiovascular surgery in 2010. Patches (e.g., TachoSil® [Nycomed Pharma], Veriset™ [Covidien], Evarrest™ [Ethicon]) composed of fibrin sealant combined with other hemostatic agents (e.g., polyglactin, oxidized regenerated cellulose) are in the early stages of clinical investigation.  

There are a number of safety concerns with fibrin sealants. The biggest concern with fibrin sealants is the potential risk of blood-borne infection from pooled plasma. This risk is reduced by screening donors and testing donor blood and in commercial products through various purification and viral inactivation processes. However, this would not be a feasible or practical option in LRS. Additional risks of use of fibrin sealant with bovine thrombin include antibody formation and swelling. Adverse effects include possible allergic reactions to milk or bovine by-products and higher concentrations of thrombin in the sealant increasing the rate of thrombosis. TISSEEL® contains aprotinin, a protein associated with anaphylactic reactions.

The following fibrin sealant LHAs have been used to control bleeding due to various causes of PPH:

- Hemostatic collagen fleece (TachoSil®): intractable lower uterine segment hemorrhage after placenta praevia, hemorrhage at the uterine incision site.
- Biologically active, fibrin sealant (TISSEEL®): complicated obstetric laceration, multiple vaginal lacerations resulting from rotational forceps delivery.

Cost is another limitation of this category of local hemostatic agents. Prices of these agents range from US$400 to US$800 per application. Although more expensive, fibrin sealants have significantly higher rates of hemostatic control compared with gelatin-thrombin combinations.

**Antifibrinolytic agents†**

TXA, an antifibrinolytic agent, has been available for decades and has been used intravenously (IV) to reduce blood loss in surgery by preventing clot breakdown (fibrinolysis). Although there have been no RCTs on the use of TXA for the treatment of PPH following vaginal delivery that address the priority outcomes, the World Health Organization (WHO) recommended the use of parenteral TXA for treatment for PPH if: “(i) administration of oxytocin, followed by second-line treatment options and prostaglandins, has failed to stop the bleeding; or (ii) it is thought that the bleeding may be partly due to trauma.” There is also interesting new evidence showing successful use of IV TXA for prevention of PPH.  

† The landscape is focused on LHAs and will not describe or discuss the research on systemic TXA.
However, concerns about possible thromboembolic events with parenteral administration of TXA have stimulated increasing interest in its topical use. The direct application of TXA to the bleeding surface has the potential to reduce bleeding with minimal systemic effects and has the additional advantage that it could be used by providers not authorized to give injections. A systematic literature review of the use of topical TXA for bleeding identified 28 trials that indicated that local application of TXA reduces bleeding after surgery (cardiac, thoracic, spinal, knee, or head and neck surgery).\(^\text{42}\) In most of the trials, TXA was administered in saline solution directly onto the bleeding site, either by pouring or spraying into the surgical wound or in some cases as a gel.\(^\text{43}\) To date, local use of TXA has not been investigated for obstetric complications and PPH.

Hemostasis is typically achieved in 3–5 minutes after administration. When used systemically, TXA has a thromboembolic effect; it is not certain whether or by what degree this effect is limited by topical application, but the risk must be considered when making a decision to use topical TXA. Preparation requires mixing TXA with a saline solution, which is straightforward but requires injection skills. Both a gel and spray are available for use topically, and application to the bleeding site is not complicated.

TXA does not require refrigeration, which is a big advantage. In general, it is recommended that TXA be stored at RT away from direct heat and light. At additional advantage is that it is stable for up to 12 weeks at temperatures up to 50ºC.

Generic TXA is manufactured by 65 companies.\(^\text{4}\) The cost of the drug will depend on the manufacturer, the country of purchase, and the presentation of the drug: tablet, capsule, syrup, cream, gel, ointment, liquid, or injection. The CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) studied the cost-effectiveness of administering TXA to trauma patients and found that the cost of giving TXA to 1,000 patients was Int$17,483 in Tanzania, Int$19,550 in India, and Int$30,830 in the United Kingdom.\(^\text{44}\) Use of the product would, therefore, most likely be under Int$100.

**Nonfibrin sealants and tissue adhesives**

Tissue adhesives are mostly used as an alternative to sutures for tissue approximation but can be used to promote hemostasis as well. An advantage of tissue adhesives is that they join tissues without need for an intact clotting mechanism and polymerize within approximately 30 seconds. A Cochrane review provided evidence that tissue adhesives are an option to sutures, staples, and adhesive strips for the management of simple traumatic lacerations.\(^\text{45}\) Providers using them need to have a good understanding of preparation time and application techniques. To date these agents have not been investigated for obstetric complications and PPH.

Two examples of nonfibrin sealants/tissue adhesives are FocalSeal™ (Genzyme Biosurgery) and CoSeal® (Baxter Healthcare). These are both polyethylene glycol (PEG)-based agents. FocalSeal™ has been used largely for sealing air leaks in thoracic surgery. It requires activation by a light source, and is, therefore, probably not appropriate for use in LRS for PPH due to equipment cost. CoSeal® is a synthetic

\(^{1}\) [http://www.medindia.net/drug-price/tranexamic-acid.htm](http://www.medindia.net/drug-price/tranexamic-acid.htm)
hydrogel that acts as a sealant. The hydrogel is formed at the time of administration when PEG powder, liquid sodium phosphate buffer, and a desiccant are mixed together. At an approximate cost of US$150 to US$200/ml, CoSeal® is also likely not appropriate for use in LRS.

More information about mechanism of action and efficacy is needed in this group of newer PEG polymers.

**Novel local hemostatic agents**

A polymeric hemostatic agent is a relatively newer category of LHA with little currently available trial data. However, it offers additional options and might be lower in cost. The products available are BioHemostat™ (Hemodyne), which is a mechanical LHA dressing that once inserted into the site of bleeding absorbs fluid and expands, creating backpressure to stop bleeding; WoundSeal® (Biolife)** is available over the counter and indicated for minor bleeding and small lacerations. A number of synthetic polymeric sealants are currently under investigation.

Another novel LHA is a peptide-based nanohaemostat, which self-assembles into a sheet of nanofibers on contact with ionic solutions. Its mechanism of action is not completely clear; it may be related to tight conformation to the wound, followed by formation of a barrier stemming the flow of blood. Importantly, it is not thought to involve the inherent clotting mechanisms and is nontoxic and nonimmunogenic. This local agent, discovered by researchers at the Massachusetts Institute of Technology and the University of Hong Kong, could be very promising and is undergoing clinical testing.

Ankaferd® blood stopper (ABS [Ankaferd Health Products]) is a new hemostatic agent that is designed for external bleeding sites. ABS comprises a standard mixture of *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, and *Urtica dioica*. It has been approved in Turkey for the management of maternal bleeding. This LHA would be dispensed as an ABS spray to control bleeding during episiotomy repair.

One other novel approach is a hemostatic intrauterine suction cup. It is an innovative medical device that is still in the proof-of-concept stage. It is introduced in the uterus and depresses the uterine walls and collapses them. The actuation of the suction cup leads to aspiration of all sides of the uterus to stop the bleeding.

**Scenarios for use of local hemostatic agents**

When a woman has PPH, there are a series of actions that must be taken to manage it prior to surgical intervention. Management options include uterine massage, uterotonic drugs, internal bimanual uterine compression, aortic compression, pressure from a uterine tamponade, suturing, compression sutures, or IV hemostatic agents (e.g., TXA, and recombinant activated factor VIIa). In cases where bleeding

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2. **Formally known as Quick Relief (QR™).**
continues in spite of management, it would be beneficial to have an intervention that could limit blood loss and the possibility of disseminated intravascular coagulation and allow time for uterotonic drugs to act. LHAs have a potential to serve this purpose and, if adequate evidence were available, could be integrated into existing algorithms for management of PPH (see Appendix C).

An advantage of LHAs, when compared with other technologies to manage PPH, is that they can be used in cases of uterine atony, lacerations, or anticoagulation rather than being confined to managing only one cause of PPH (e.g., uterine atony). LHAs could be used in the following scenarios depending on the primary causes of PPH deaths in any given country, province, district, or facility:

- **Tone (uterine atony):**
  
  Some case studies have found that bleeding resolves when LHAs are placed directly on the placental implantation site when conventional treatments for uterine atony (uterotonic agents, uterine balloon tamponade [UBT], vessel ligation, uterine compression sutures, over-sewing placental bed bleeding sites) have failed. If the uterus does not contract adequately after delivery of the placenta, blood vessels at the implantation site bleed freely and hemorrhage occurs. LHAs can cause hemostasis until uterotonic drugs can begin to induce uterine contractions in both the upper and lower segments of the uterus.

  We assume that LHAs could be used for this purpose at all points of care but would require a mechanism to transport the LHA to the placental site, training to apply it, and means to ensure sterility during application. It is possible that application of an LHA could replace bimanual uterine compression or UBT.

  LHAs could also be used during interventional radiology procedures, including uterine arterial embolization for uterine atony. This would, of course, require specialized physicians and equipment to perform the procedure and would, therefore, be restricted to hospitals providing comprehensive emergency obstetric care.

- **Trauma (lacerations, hematomas, uterine inversion, and uterine rupture):**
  
  LHAs could serve as a first aid measure for providers not skilled to suture or in cases of complicated obstetric lacerations if they are safe, effective, affordable, can be safely applied by less-skilled providers, are quickly and easily prepared and applied, and do not require special conditions for storage. LHAs could theoretically be used in the community setting by community health workers and traditional birth attendants for use in treating simple genital lacerations.

  Nonfibrin/tissue sealants could be used for uncomplicated, first- or second-degree genital lacerations and would theoretically obviate the need for suturing and induce hemostasis. LHAs that induce hemostasis but do not seal the wound would still require that the woman be transferred to a facility where the laceration could be sutured. It would be necessary to ensure that community-based
providers are able to distinguish between lacerations that require assessment and repair by a skilled provider.

In cases of complicated genital lacerations, including third- or fourth-degree tears, where repair of sphincters and muscle layers is necessary, LHAs could be applied to minimize bleeding until the lacerations could be repaired by a skilled provider competent to repair them.

LHAs can be used for bleeding during or after cesarean operation. Bleeding during or after cesarean may be due to uterine atony, lacerations and tears if the initial incision was not wide enough for the baby to be lifted out, accidental nicking of large arteries and veins near the uterus, or inadequate suturing. Ongoing bleeding despite routine treatment may also occur during cesarean for placenta praevia/accreta/increta.

We assume that LHAs could be used for this purpose at all points of care but would require guidelines on specific use by a cadre of providers, training to apply it, and means to ensure sterility during application.

- **Thrombin (clotting disorders):**

  Diagnosis of a coagulopathy can be done using the bedside clotting test that does not require special laboratory equipment or specialized training. Providers at all facility levels should, therefore, be able to diagnose coagulopathy in cases of PPH or oozing not responding to conventional treatment. While definitive management of a clotting disorder should occur at a comprehensive emergency obstetric care facility, LHAs may be used to induce hemostasis until definitive treatment can be provided by a specialist physician.

  We assume that LHAs could be used for this purpose at all facilities providing maternity services with staff able to perform the bedside clotting test but would require guidelines on use, training to perform the bedside clotting test and apply LHAs for this purpose, and means to ensure sterility during application.

**Gap analysis**

Many LHAs are available, and there has been an upsurge of interest in their use for PPH. Although the use of LHAs for various surgical applications has generated a significant body of literature, there are few rigorous randomized trials for their use in PPH or in LRS. It is, therefore, difficult to tell clinicians, policymakers, or program managers whether any given LHA is more effective, safer, or more cost-effective than another LHA or than products/interventions currently being used.

In addition, there is widespread variation in and no international guidelines for their use. Knowledge deficits related to use of LHAs for management of PPH in LRS, include:
• Lack of adequate clinical trial data to guide providers in managing their patients or develop clinical guidelines for their use in cases of PPH.

• Lack of uniform outcome measures to judge efficacy and few studies establishing the efficacy of LHAs for PPH.

• Lack of studies to compare efficacy of LHAs and conservative treatments for PPH (e.g., direct pressure, UBT, and systemic hemostatic agents).

• Insufficient studies comparing the various LHAs to guide choice of the most relevant LHAs for each cause of PPH.

• Limited safety data on use of LHAs for PPH, including safety when combined with other treatments for PPH and coagulopathies.

• Insufficient data on which LHAs have the least side effects when used by less-skilled providers.

• Limited understanding of the biological effects of LHAs in women with PPH to help determine who should receive it.

• Lack of data on cost-effectiveness of LHAs for different scenarios of use.

**Investment opportunities**

There are good reasons to consider adding LHAs to PPH management programs: many LHAs are currently available, LHAs are generally capable of effectively achieving hemostasis within 10 minutes or less, some are relatively inexpensive and easy to prepare and apply, and there is experience with some in managing PPH. They would have measurable impact if they could be introduced at points of care where treatment options are currently limited because of lack of skilled providers or lack of infrastructure and/or equipment. LHAs could be used:

• As “first aid” to induce hemostasis until suturing can be performed at points of care where providers are not competent to suture or are not competent/confident to suture complicated obstetric lacerations.

• As first-line treatment for bleeding occurring in hard-to-reach areas.

• As adjunct treatment to induce hemostasis:
  - At the placental implantation site until uterine contractions are induced by uterotonic drugs.
  - In cases of complicated lacerations when suturing is difficult.
  - In cases of bleeding due to coagulopathy.

• During interventional radiology procedures, including uterine arterial embolization for uterine atony.

Regrettably, there is widespread practice variation, guidelines are vague, LHAs are not matched to the type of hemorrhage, and safety data are not fully recorded or recognized. Several investment
opportunities over a period of the next one to three years exist to support the use of LHAs for PPH in LRS, including:

*Investment opportunity #1: Gain consensus and build evidence*

- Convene a multidisciplinary panel of experts, preferably with experience using LHAs for PPH, to:
  - Gain consensus around a rational approach to LHA use by: (1) identifying use scenarios of LHAs for PPH and (2) gaining consensus on possible uses in LRS.
  - Gain consensus on steps required for inclusion of LHAs in international clinical guidelines for management of PPH, including key research questions and study designs to support gathering evidence on use of LHAs for PPH in LRS.

The consultation would specifically aim to increase awareness of LHAs for PPH, propel LHAs to the forefront of the global agenda on PPH management protocols, and guide the level and kind of evidence that would be required.

- Facilitate the development of a community of practice for LHAs to:
  - Rationalize and strengthen research efforts.
  - Track development of promising novel LHAs. A number of novel approaches and methods are currently under investigation, but most of the work is either in early proof-of-concept stages or in early trials. Special attention will be given to LHAs that are safe, easy to use, low cost, and address the identified scenarios of use where LHAs for PPH would be most impactful.

- Support comparative efficacy and safety trials for LHAs that have already been used for PPH: Chitosan-covered gauze (Arsenal foam, XSTAT™), kaolin-infused gauze (QuikClot®), smectite-impregnated gauze or patches, topical fibrin sealants (TachoSil®, TISSEEL® and the novel ABS). Studies should focus on the mechanical LHAs that when compared to other categories of LHAs seem to be the safest, lowest cost, most heat stable, and easiest to prepare and use.

- Investigate the efficacy, safety, and cost-effectiveness of:
  - Nonfibrin sealant/tissue adhesives for use in cases of simple genital lacerations and to compare their efficacy and safety with suturing.
  - Local application of TXA for PPH.

These studies need to track bleeding and other patient outcomes and contribute to the refinement of practice guidelines and choice of LHAs that can be safely and effectively used in different scenarios of use in LRS.

*Investment opportunity #2: Use expert consensus and/or evidence for guideline development*

- If there is either adequate evidence or consensus by experts on use:
- Initiate critical steps to advance policy and programmatic plans to accelerate market penetration and uptake, ensure commercial sustainability, ensure LRS affordability, and ensure global access to the technology.

- Advocate promoting inclusion in the WHO guidelines for PPH management and global and in-country regulatory approvals.

- Develop and disseminate a simple decision-making tool to assist program managers and countries in choosing a rational selection of LHAs by type of provider and point of care.

- Develop and disseminate algorithms for management of PPH that include use of LHAs (see Appendix C).

- Develop and disseminate a simple decision-making tool to assist the provider in choosing the most appropriate LHA by site and type of hemorrhage. For example, a decision tree could be developed, similar to that developed by Shander et al.\textsuperscript{32} (see Figure 1), to choose the type of LHA based on severity of bleeding and whether bleeding is local or diffuse.

**Figure 1. Selection of local hemostatic agent by extent of bleeding.**

- Once optimal LHAs have been identified and tested, conduct operations research to demonstrate acceptability, feasibility, cost-effectiveness, and optimal scenarios of introducing them. This information will assist ministries of health and donors to understand these products and their advantages, disadvantages, complications, costs (financial and system costs), and optimal ways to scale up their use.
Investment opportunity #3: Develop market for and expand use of existing products

- Build a global constituency for LHAs by linking with established networks to support LHA development, introduction, and scale-up. Achieving access to lifesaving technologies is best supported by enlisting and organizing influential and invested champions of a new technology to leverage resources, share information, and coordinate activities to ensure efficient and aligned outcomes.

- Characterize the potential market opportunity for LHAs to ensure that product development activities and decisions are well informed by a robust understanding of key market drivers. Improving the evidence base will ensure that the most effective technologies are adequately guided and accelerated toward global and regional introduction.

- Characterize readiness to sustainably introduce and integrate LHAs to proactively establish an understanding of conditions that will be required and country-level activities necessary for country-level introduction and transition to scale-up.

- Where possible, promote technology transfer to manufacturers in LRS to facilitate access and reduce cost.

Investment opportunity #4: Develop new products that are appropriate for LRS

- Consider adaptation of existing LHAs to: (1) simplify preparation, (2) improve heat stability, or (3) simplify application.

- Consider development of LHAs that are designed for use in LRS.
References


