**Clinical question.**

In patients with severe external bleeding (P), does the use of topical hemostatic agents plus standard therapy (I), when compared with standard therapy alone (C), improve control of hemorrhage (O)?

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Intervention/therapy

**State if this is a proposed new topic or revision of existing worksheet:** New

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

- **Cochrane:** (MeSH descriptor **Hemorrhage**, this term only OR (Hemorrhage):ti,ab,kw OR (Bleeding):ti,ab,kw AND (topical hemostatic agents):ti,ab,kw
- **Medline:** ("Hemostatics"[Mesh:noexp] AND "Hemorrhage"[Mesh:noexp]) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])
- **EMBASE:** 'bleeding'/mj AND 'hemostatic agent'/exp/mj AND (‘topical’/de OR topical) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)
- **AHA EndNote X master library, review of references from articles, forward search using SCOPUS and Google scholar.**

**State inclusion and exclusion criteria**

Inclusion criteria: articles located in electronic databases that met the search strategy, and other articles located through bibliographies or ‘cited by’ in SCOPUS that addressed the clinical question. Exclusion criteria: articles that represented duplicate publications from the same study, studies that did not address severe external bleeding, and review articles or guidelines.

**Number of articles/sources meeting criteria for further review:**

Thirty-three studies met criteria for further review. Of these, zero were LOE1, zero were LOE 2, zero were LOE 3, four were LOE 4, and 29 were LOE 5.
### Summary of evidence

#### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>A = Return of Spontaneous Circulation</td>
<td>E1 = Controlled bleeding</td>
</tr>
<tr>
<td>B = Survival of event</td>
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<tr>
<td>C = Survival to Hospital Discharge</td>
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<td>D = Intact neurological survival</td>
<td>E4 = Improved blood pressure</td>
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<td>E3 = Reduced blood loss</td>
<td>Italics = Animal studies</td>
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<td>Galownia, 2006, 61, E1</td>
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### Evidence Neutral to Clinical question

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**Outcomes**
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*Englehart 2008, 884, B
Walters 2006, 1107, B*

### Evidence Opposing Clinical Question

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*Italicics = Animal studies*
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: (please include implementation considerations including at a minimum training, environment and availability):

**DISCUSSION:** All of the published, controlled studies on the efficacy of topical hemostatic agents use animal models. There are a few published case series in humans, but these reports lack control groups.

- Published reports use a wide variety of topical hemostatic agents with diverse characteristics. Some are packaged as fairly rigid dressings, others are flexible dressings, while still others are available as granules that are poured into a wound or placed in a permeable bag for use in a bleeding site.
- All of the published animal studies, along with the human case series, show improved outcomes for topical hemostatic agents as compared to standard care.
- There has yet to be a study that indicates which topical hemostatic agent is the most efficacious, and although hemostatic agents may be life-saving, there is strong evidence some agents can cause significant morbidity.

**Acknowledgements:** John Holcomb, MD, FACS and Sarah Thomas assisted with the review of this worksheet.

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**Citation List**


   **LOE 5.** The quality of this study was good. The study used a femoral artery injury in swine that was allowed to bleed for 45 seconds. Each of the tested products was then applied to the bleeding wound. Use of an Army field bandage & QC did not obtain hemostasis. CD enabled hemostasis once, but there was rebleed. FSD facilitated hemostasis in 67% of the cases, reduced blood loss, resulted in better mean arterial blood pressure, and improved survival rates.


   **LOE 5.** The quality of this study was good. This randomized study used a complex groin injury in swine that was allowed to bleed for three minutes. The wounds then received no dressing, standard dressings, or a ZH. The ZH reduced mortality and controlled hemorrhage. Variations of the ZH decreased temperature at the wound site.


   **LOE 5.** The quality of this study was good. This study used a complex groin injury in swine that was allowed to bleed for five minutes. The tested products were then administered. Saline was used to resuscitate after 30 minutes. Only QC showed a significant increase in survival rate, but there was no significant decrease in blood loss.

LOE 5. The quality of this study was good. This study used a complex groin injury in swine that was allowed to bleed for five minutes. The tested products were then administered. Saline was used to resuscitate after 30 minutes. Only QC showed a significant increase in survival rate, but there was no significant decrease in blood loss.


LOE 5. The quality of this study was good. This randomized study allowed a femoral artery transection in swine to bleed for two minutes. Afterwards, 11 different treatments were administered. The randomization scheme was not described and it is unclear if the randomization list was concealed. All the animals entering the study were accounted for at the conclusion and all animals were analyzed in the groups to which they were randomized. Investigators were not blinded to treatment. Aside from experimental treatment, the groups were treated equally. Fifteen minutes post-treatment, 500 mL of Hextend was administered over 30 minutes. Baseline characteristics and pre-treatment blood loss were similar between groups. For the outcomes of survival, any hemostatic dressing was significantly better than standard gauze, and WS, CEL, X-Sponge (XS) and ACS+ significantly outperformed the worst four agents: Polymem FP-21, Alpha bandage, Chitoflex, and BloodStop. WS, CEL, InstaClot, ACS+, Alpha bandage, and XS performed best at controlling bleeding. The other five hemostatic agents performed similar to standard dressing, with regard to bleeding. WS, XS, IC, and CEL performed the best at preventing rebleeding. This research was funded by MARCORSYSCOM.


LOE 5. The quality of this randomized animal study was good. This study allowed a femoral artery puncture in swine to bleed freely for 45 seconds. Afterwards, 11 different treatments were used. The randomization scheme was not described and it is unclear if the randomization list was concealed. All animals entering the study were accounted for at the conclusion and all animals were analyzed in the groups to which they were randomized. Investigators were not blinded to treatment. Aside from experimental treatment, the groups were treated equally. Fifteen minutes post-treatment, 500 mL of Hextend was administered over 30 minutes. Baseline characteristics and pre-treatment blood loss were similar between groups. Any hemostatic dressing was significantly better than standard gauze, and WS, CEL, X-Sponge (XS) and ACS+ significantly outperformed the worst four agents: Polymem FP-21, Alpha bandage, Chitoflex, and BloodStop. WS, CEL, InstaClot, ACS+, and XS performed best at controlling bleeding. The other five hemostatic agents performed similar to standard dressing. WS and CEL performed the best at preventing rebleeding. Funded by MARCORSYSCOM.


LOE 5. This randomized animal study was of fair quality. The study consisted of two experiments. In the first, following femoral transection that bled freely for two minutes, the swine were randomized to either ACS or ACS+ and compared to SD. The wound was continuously suctioned and wound temperature and bleeding control were measured. In the second experiment, following femoral transection that bled freely for two minutes, ACS was compared to SD but the wound was not suctioned. Again, wound temperature and bleeding control were measured. The randomization scheme was not described and it is unclear if the randomization list
was concealed. All the animals entering the study were accounted for at the conclusion and were analyzed in
the groups to which they were randomized. Investigators were not blinded to treatment. Aside from
experimental treatment, the groups were treated equally. Baseline characteristics were similar between
groups. In both experiments ACS and ACS+ controlled bleeding better than SD, while SD maintained a lower
wound temperature. Between the non SD products, temperature increased in evacuated wounds less with
ACS+ than ACS, and temperature increased less with ACS than ACS+ in blood-filled wounds. No funding
source was disclosed, although investigators were employees of the US Navy.

8. Arnaud F, Tomori T, Saito R, McKeague A, Prusaczyk WK, McCarron RM. Comparative efficacy of
granular and bagged formulations of the hemostatic agent QuikClot. Journal of Trauma - Injury, Infection and
Critical Care. 2007;63(4):775-82.

LOE 5. This study was of good quality. This randomized animal study allowed a groin injury in swine to bleed
freely for three minutes. Afterwards, one of the four treatments were administered for five minutes and
observed for four hours. Both QC and ACS offered improved survival and hemostasis compared to SD.


LOE 4. This study was of poor quality. This study observed the effectiveness of HemCon Bandage following its
use on a wound when conventional treatment would not control bleeding. Data from 34 cases showed
hemorrhage was controlled in 79% of the cases.

hemostatic agent to a commercially available granular zeolite agent for hemostasis in a swine model of lethal

LOE 5. This randomized animal study was of good quality. In this study, 14 swine were pre-treated with
splenectomy and crystalloids. Further crystalloid infusions were provided during resuscitation after a femoral
artery transection that bled freely for 45 seconds. The wound cavity was not suctioned. Evidence showed
100% survival using WS as compared to QC where no animals survived to 120 minutes. Blood loss was also
less for WS. There was no comparison to SD. It was not stated whether the randomization list was concealed.
All animals were accounted for at the conclusion of the study. Investigators were not blinded. The groups
were treated equally except for the product applied and the groups were similar at the start of the trial. The
study was funded by the manufacturer. One author is the president and CEO of the manufacturer. Another
author has filed for intellectual property rights on the product.

11. Connolly RJ. Application of the poly-N-acetyl glucosamine-derived rapid deployment hemostat trauma

LOE 5. This study was of poor quality. In this study a femoral artery and an abdominal aorta wound was
made in swine and allowed to bleed for 30 seconds before either RDH, a fibrin sealant dressing, or gauze were
administered. The swine were resuscitated using saline, however the study did not account for the different
volumes of saline between the treated and control groups. The RDH bandage did show a decrease in blood
loss compared to the fibrin and gauze.

**LOE 5.** This animal study was of fair quality. There was no mention of randomization in the study. Sixteen rabbits received a femoral artery wound and were treated with silver exchanged calcium doped ordered mesoporous silica spheres vs controls. The treatment groups had better bleeding control and reduced blood loss compared to SD. The comparison groups were clearly defined. The outcomes were measured in the same unblinded way in each group. The study was funded by the National Natural Science Foundation of China, the Program of Shanghai Subject Chief Scientist, and Shanghai Nanotechnology Special Foundation.


**LOE 5.** This randomized animal study was of poor quality. In this study, 30 swine received a complex groin injury and were administered TraumaStat, HemCon or standard gauze. The wound was allowed to bleed freely for 30 seconds followed by five minutes of pressure then fluid resusitation. HemCon decreased blood loss, but there were no power calculations and there was the significant possibility for a type two error.


**LOE 5.** This study was of good quality. In rats a 24 guage needle punctured the femoral artery and bleeding supression was attempted either with MPH or compression. The groups were treated equally and began as equivalent groups, however was achieved with MPH while it was not achieved with compression alone.


*Only abstract available for review.* **LOE 5.** In this animal model study, a groin laceration was administered to 16 swine and QC-ACS or standard gauze was applied to the wound. QC-ACS reduced blood loss when compared to SD. The funding status of this research is unknown.


**LOE 5.** The quality of this animal model study was good. Following a femoral artery injury, 30 pigs were treated with tourniquet alone, a modified ethyl-2-cyanoacrylate-based aerosol spray (ECA) plus tourniquet, or ECA, plus tourniquet, plus wound cleaning. ECA decreased blood loss and achieved hemostasis. There was no support listed but the authors developed the ECA product.

LOE 5. *This in vitro study was of poor quality. This bench trial with mouse blood demonstrated that VPI-5:Ca^{2+} was equivalent to QC for hemostasis, while allowing half the rise in temperature at the wound site. The research was funded by the Caltech SURF program.*


LOE 5. *This animal study was of good quality. In this study, 14 swine received arterial punctures after which either gauze or HC were administered. HC showed greater hemostatic ability as well as less rebleeding than the gauze.*


LOE 5. *This study was of good quality. In this study 18 goats received a ballistic extremity injury and administered either gauze or DFSD. Compared to regular gauze, DFSD significantly decreased blood loss while improving blood pressure.*


LOE 5. *This animal study was of good quality. In this study swine received two femoral artery wounds. A fibrin sealant was applied to one wound while a control dressing was applied to the other. There was no free bleeding period and resuscitation was accomplished with a crystalloid. Blood loss was significantly less with the FSD as compared with the control dressing. No funding was described, but the authors are employees of the US Army or the American Red Cross, who manufactures the FSD.*


LOE 5. *This study was of good quality. After swine received femoral artery injuries that were allowed to bleed uncontrollably for 45 seconds, a test agent or control product was administered to the wound. The study desisted in testing ACS as it failed to control bleeding in six attempts. WS, SQR, and CX all exhibited greater hemostatic ability than HC, with WS more efficacious than SQR and SQR more efficacious than CX. A significant rise in temperature at the wound site was observed only with SQR. WS and SQR also improved clotting, while CX and HC showed no effect on coagulation. This is potentially a key study and was funded by the US Army.*

LOE 5. This study was of good quality. In this randomized study 48 swine received a complex groin injury followed by four possible treatments. CX improved survival and reduced rebleeding in all test subjects, while QC and HC also improved survival and reduced rebleeding when compared to standard treatment, although to a lesser extent than CX.


Only abstract was available for review. LOE 5. This randomized animal study administered an arterial hemorrhage to swine to which gauze containing fibrinogen and thrombin were applied. The fibrin bandages maintained arterial pressure and decreased blood loss as compared to SD.


LOE 5. This study was of good quality. In this study swine received a complex groin injury to which one of five treatments was administered after three minutes of uncontrolled bleeding. Of the treatments, the zeolite hemostat decreased blood loss, improved survival, and when Ag and Zn were added, prevented a rise in temperature at the wound site. This study was funded by the People's Liberation Army.


LOE 4. This study was of poor quality. In this study four cases reported thermal injuries in patients receiving zeolite hemostats. All of the subjects survived to hospital discharge. The outcomes of the cases were not measured objectively and confounders were not identified. In addition, follow-up was not sufficiently long or complete.


LOE 4. This study was of poor quality. In this study, participants reported on their use of QC in several settings. The participants reported a 92% effectiveness in stopping blood loss. The survey, however, was sent to participants after 'word of mouth' reports informed the researchers of incidents of use. There was no systematic evaluation or follow-up.


LOE 5. This study was of good quality. In this study 23 swine received one of three treatments following a femoral vessel transection. The wound was allowed to bleed uncontrollably for 30 seconds. Following this the randomized treatment was administered. There was no description of the randomization scheme. There was no
significant difference in mortality between the groups, but TS controlled hemorrhage better than Chitoflex or standard gauze. The study was funded by manufacturer.


LOE 5. This study was of poor quality. In this study goats received a femoral artery injury after which standard treatment was administered followed by one of three additional treatments. DS showed the greatest hemostatic ability.


LOE 5. This study was of good quality. In this study, swine received a femoral artery wound and bled freely for three minutes after which either a standards dressing or SEHP were administered. The SEHP exhibited greater survival rates and less blood loss than standard guaze. The funding source of this research was not disclosed, however three of the authors are employees of the manufacturer of the product being tested.


LOE 5. This study was of poor quality. In this study goats received a femoral artery wound to their thigh, which had a tourniquet. After the wound was administered the tourniquet was released and BioFoam was applied to the wound. The results showed no increase in survival in treated animals as compared with untreated animals.


LOE 5. This study was of good quality. In this study 25 swine received a femoral artery injury to which one of the treatments was applied after 45 seconds of uncontrolled bleeding. WS had the greatest increase in survival and the greatest decrease in blood loss. Funded by US Army Med. Research and Material Command.


LOE 4. This study was of poor quality. The study analyzed reports on 68 cases of the use of HemCon dressings in combat settings. In nearly 2/3 of the cases the HemCon dressing was administered after gauze failed to stop wound hemorrhage. In 62/64 cases the HemCon controlled the bleeding.

LOE 5. This animal study was of fair quality. In this study, swine received multiple traumatic injuries to which hemostatic agents were applied. This study only discusses the granular mineral agent used in the research. Although blood loss was reduced in most of the injuries, the focus of the study was on the increase in temperature at the wound site. This was a US Air Force study.