Trauma is a leading cause of morbidity and mortality. Uncontrolled hemorrhage related to the traumatic event is often the major cause of complications and death. The use of hemostatic agents may be one of the easiest and most effective methods of treating hemorrhage. The US military recommends a hemostatic combat gauze (QuikClot Combat Gauze) as the first-line hemostatic agent for use in treatment of severe hemorrhage. This review provides essential information for evidence-based use of this agent. The PICO (patient, intervention, comparison, outcome) question guiding this search for evidence was: Is QuikClot Combat Gauze, a hemostatic agent, effective and safe in controlling hemorrhage in trauma patients in the prehospital setting? The evidence appraised was a combination of lower-level human and animal research. It did not conclusively demonstrate that this combat gauze is an effective hemostatic agent for use in trauma patients, but the results are promising in supporting its use. The evidence does not describe serious side effects, exothermic reaction, and thromboemboli formation associated with other hemostatic agents. Further investigation to determine the effectiveness of hemostatic agents, specifically QuikClot Combat Gauze, in the management of trauma casualties in the prehospital setting is required. These should include large-scale, multicenter, prehospital randomized controlled trials.

Keywords: Combat gauze, hemorrhage control, hemostatic agent, trauma, QuikClot Combat Gauze.
setting. Traumatic injuries may occur in anatomic locations where tourniquets cannot be used or employed effectively. Hemostatic agents have been developed to control hemorrhage in these areas. Also, the effectiveness of tourniquets may be improved, with reduced morbidity and mortality, if they are used in conjunction with these hemostatic agents.11,12

Pusateri et al13 outlined the ideal qualities of hemostatic agents for civilian and military use (Table 1). The current hemostatic agents include zeolite, smectite, kaolin, chitosan, and plant-derived polysaccharides.10,14-18 These hemostatic agents have been investigated in animal models. Investigations produced inconsistent and conflicting results regarding the effectiveness of hemostatic agents in controlling hemorrhage, which indicate the need for additional investigation.10,13,17-23

Two agents that were widely used by the US military, QuikClot (Z-Medica) and WoundStat (TraumaCure), have been removed from the inventory because of potential complications, specifically tissue injury to patient and provider and microemboli formation.15,16,24 QuikClot is composed of zeolite and WoundStat is composed of smectite, and both are granular products.13,16,24

This review provides essential information for evidence-based use of a newer hemostatic agent, QuikClot Combat Gauze (Z-Medica). This agent is manufactured by the same company as QuikClot but contains a different hemostatic agent. QuikClot Combat Gauze is composed of a kaolin-impregnated rayon and polyester hemostatic dressing (Figure).25

Materials and Methods

- **The PICO Question.** “PICO” is a common approach in evidence-based practice used to generate a well-built, clinically focused question from a specific patient scenario. It is a mnemonic describing the central components of focused question generation, with P indicating patient or problem being addressed; I, intervention or exposure being considered; C, comparison intervention or exposure when relevant; and O, clinical outcome.26,27 The PICO question guiding this search for evidence was: Is the hemostatic agent QuikClot Combat Gauze effective and safe in controlling hemorrhage in trauma patients in the prehospital setting?

Hemostatic agents have evolved from first-generation granular or fine powders such as QuikClot, to second-generation wafers and sponges and to the newest generation of impregnated hemostatic dressings such as QuikClot Combat Gauze. The dressings are designed to simplify application and decrease complications. The Committee on TCCC recommends QuikClot Combat Gauze as the first-line hemostatic agent for treatment of severe hemorrhage.11

- **Search Strategy.** The search for evidence used the following approaches: online medical literature databases, ancestry approach, and informal networking. MEDLINE, PubMed, and The Cochrane Database of Systematic Reviews (2002 to December 2012) were searched for relevant evidence using the following search terms alone and in combination: hemostatic agents, QuikClot, QuikClot Combat Gauze, and hemorrhage control. Each reference list in located sources was examined for additional sources. Informal surveys of experts in prehospital care helped identify further resources. The strategy was revised in an ongoing fashion to optimize effectiveness and relevance.

The inclusion criteria were English-language evidence addressing the PICO question published in peer-reviewed journals in full text form, including evidence from both animal and human models. Evidence from lower-level case reports and case series was included because of the suspected lack of higher-level human evidence. Evidence using animal models was included because of the suspected small number of sources available involving humans related to the ethics involved in conducting human research with trauma patients in prehospital settings.

Results

The search revealed 103 sources of evidence, with 11 meeting the inclusion criteria after review and removal of duplicates. All 8 randomized controlled trials
(RCTs)\textsuperscript{16,28-34} examining QuikClot Combat Gauze that met the inclusion criteria used an animal model. The remaining 3 sources found involved human subjects: 1 case series\textsuperscript{35} and 2 case reports.\textsuperscript{36,37} The evidence was appraised by the method proposed by Melynk and Fineout-Overholt\textsuperscript{38} and is presented in Tables 2 and 3.

A systematic review was located comparing the relative efficacy and safety of available hemostatic agents relevant to prehospital emergency medical treatment but did not exclusively examine evidence investigating QuikClot...
Combat Gauze. It did not meet the inclusion criteria because it referenced only 1 RCT investigating QuikClot Combat Gauze out of greater than 100 evidence sources. This RCT was appraised separately in this review.

**Appraisal of RCTs Involving a Porcine Model.** All the RCTs examining QuikClot Combat Gauze used a porcine model (Table 2). There is evidence that swine provide an excellent model for investigating hemorrhagic shock and resuscitation because their cardiovascular anatomy and physiology are similar to humans. The studies used different types of injury or hemorrhage models, and all varied in their methods, including splenectomy, unrestricted bleeding time, fluid resuscitation, endpoints, and outcomes. Common themes of these models were anatomic location, arterial, or arterial and venous hemorrhage. These included femoral artery punch, femoral artery and vein transection, femoral artery and vein transection with hemodilution, femoral artery and vein transection with movement, carotid artery and jugular vein transection, and subclavian artery and vein transection.

The RCT investigators examined multiple outcomes: survival, blood loss, resuscitation fluid amounts, hemostasis with limb movement, and vessel patency. However, the outcomes were measured differently in individual studies. For example, survival was defined as up to 180 minutes in 2 studies compared with 120 minutes and 60 minutes in other investigations. All investigators of the studies performed a power analysis to determine sample sizes and randomly assigned subjects to groups, but there was no blinding. Based on statistical analysis in the individual RCTs, the control and treatment groups were equivalent. In general, these studies were rigorously conducted, but comparison and/or meta-analysis would be difficult because of the heterogeneity in models and outcomes. Additionally, animal research generally provides low-level evidence, falling below editorials and expert opinion in the hierarchy of evidentiary relevance.

**Appraisal of Case Series and Case Reports.** A human case series and 2 human case reports investigating QuikClot Combat Gauze are described in Table 3. The case series reported use of QuikClot Combat Gauze during the Israel Defense Force experience in the Gaza Strip in 2009. Fourteen cases of QuikClot Combat Gauze use were reported and reviewed from 56 hematostatic interventions (42 tourniquets and 14 hemostatic dressings) in 35 human casualties. Data collection was accomplished by interviewing injured personnel and all associated medical providers. The authors acknowledged a possible recall bias and limited sample size. The case reports detailed 2 uses of QuikClot Combat Gauze to control different types of hemorrhage.

Case reports and case series are prone to numerous types of bias, including recall and publication bias. The reported results in a given setting may not apply to other settings. The outcomes reported may not be fully related to interventions because of a lack of control of potential confounding factors. Lastly, professional journal publication favors positive outcomes and results.

**Discussion**

The evidence addressing the effectiveness of QuikClot Combat Gauze is a combination of human and animal research. Each evidence source contained limitations. The human research was low-level evidence with the potential for bias and lacked generalizability. The evidence using animal models investigating QuikClot Combat Gauze were all RCTs, but it falls lower than the human evidence in the evidence hierarchy.

**Comparison of QuikClot Combat Gauze With Other Hemostatic Agents.** All of the evidence from RCTs involved a swine model, multiple injury/hemorrhage models, investigated different outcomes, and produced mixed results (see Table 2). QuikClot Combat Gauze was found to be an effective hemostatic agent, with 6 studies reporting increased survival and/or decreased blood loss in different hemorrhage settings.
models. Furthermore, QuikClot Combat Gauze allowed more effective fluid resuscitation and produced a stronger clot withstanding movement compared with control interventions.\textsuperscript{34} However, an investigational hemostatic dressing composed of expanding minisponge technology from Oregon Biomedical Engineering Institute was statistically and clinically superior to QuikClot Combat Gauze. The expanding minisponge demonstrated improved hemostasis and survival, reducing blood loss and fluid resuscitation requirements.\textsuperscript{32} Moreover, investigators reported that advanced hemostatic dressings including QuikClot Combat Gauze do not perform better than conventional wound management in care-under-fire scenarios.\textsuperscript{31}

- **Reports of Using QuikClot Combat Gauze in Humans.** There are limited data and higher quality evidence demonstrating the effectiveness of QuikClot Combat Gauze in humans (Table 3). There are no systematic reviews with or without meta-analyses or RCTs examining hemostatic agent use or QuikClot Combat Gauze in the control of hemorrhage in humans. The only human studies investigating QuikClot Combat Gauze are a case series\textsuperscript{35} and 2 case reports.\textsuperscript{36,37} Ran et al\textsuperscript{35} reported 14 uses of QuikClot Combat Gauze with a 79% (11/14) success rate and a 93% survival rate during the Israel Defense Force experience in the Gaza Strip in 2009. QuikClot Combat Gauze was applied to the head, neck, axilla, buttocks, abdomen, back, pelvis, and extremities, with 3 failures attributed to severe soft-tissue and vascular injuries. Injuries were caused by blast or penetrating (gunshot) mechanisms in 13 (93%) of 14 cases. The 2 case reports detailed successful hemostasis after QuikClot Combat Gauze was applied because of vaginal hemorrhage\textsuperscript{36} or a bleeding leech bite.\textsuperscript{37}

**Conclusion**
The current evidence appraised for this review was a combination of findings from research using a porcine model\textsuperscript{10,28-34} and from lower-level human research.\textsuperscript{35-37} The evidence did not conclusively demonstrate that QuikClot Combat Gauze is an effective hemostatic agent for use in trauma patients, but the results were promising in supporting QuikClot Combat Gauze. In addition, the evidence did not describe serious side effects such as exothermic reactions with resulting tissue injury and thromboemboli formation associated with the earlier granular hemostatic agents (QuikClot containing zeolite and WoundStat containing smectite).\textsuperscript{13,16,24}

Further investigation is required to determine the effectiveness of hemostatic agents, specifically QuikClot Combat Gauze, in the management of trauma casualties in the prehospital setting. These studies are particularly warranted because QuikClot Combat Gauze is recommended by the Committee on TCCC.\textsuperscript{11} This research should include higher-level human studies such as large-scale, multicenter, prehospital RCTs. Such prehospital studies are difficult to conduct for ethical reasons, such as difficulty in obtaining informed consent. With proper safeguards and procedures, it is possible to conduct these important investigations.\textsuperscript{41}

**REFERENCES**