

Chapter 34

THROMBOEMBOLIC DISEASE AND MANAGEMENT OF ANTI- COAGULATION IN TRAUMA

AARON B. HOLLEY, MD*

INTRODUCTION

PATHOPHYSIOLOGY OF VENOUS THROMBOEMBOLISM IN TRAUMA PATIENTS

Effects of Massive Transfusion, Factor VIIa, and Tranexamic Acid
Prevalence of Venous Thromboembolism in Trauma Patients

PREVENTION OF VENOUS THROMBOEMBOLISM

Mechanical Prophylaxis
Chemical Prophylaxis
Neuraxial Blockade
Inferior Vena Cava Filters

SUMMARY

**Lieutenant Colonel, Medical Corps, US Army; Chief of Sleep Medicine, Walter Reed National Military Medical Center, 8901 Wisconsin Avenue, Bethesda, Maryland 20889*

INTRODUCTION

Patients who suffer from acute traumatic injuries are at significant risk for venous thromboembolism (VTE) during their recovery period. Traumatic injuries have effects on the physiologic mechanisms responsible for clot formation and resolution, making prevention and treatment challenging. In addition, trauma patients often have injuries that involve and subsequently predispose them to hemorrhage, limiting the physician's ability to prevent and treat VTE.

Patients who are injured in a combat theater have additional risk factors for the development of VTE. Massive resuscitation with component products, whole blood, and hemostatic agents such as factor VIIa and tranexamic acid may increase clotting risk. Patients spend a large part of the first 48 hours after injury traveling back to the continental United States via the air evacuation system. During this time they are intubated and sedated, sometimes paralyzed. Extubation often must be delayed, even when it may be

appropriate clinically, in order to maintain adequate control of the patient during transport, because options to make interventions during flight are limited. Although prophylaxis is often administered en route, it may be withheld for precautionary purposes in patients who have recently been resuscitated in an operating room.

After the first 48 hours, patients can spend weeks traveling to and from the operating room for wound debridement and other procedures. Although some surgeons are comfortable continuing chemical VTE prophylaxis during trips to the operating room, others are not, which results in substantial time without chemical prophylaxis. Injuries from improvised explosive devices (IEDs) may involve lower extremity amputations, preventing the regular application of sequential compression devices (SCDs) or other types of mechanical prophylaxis. Finally, when VTE does occur, treatment failure and recurrence rates are high.

PATHOPHYSIOLOGY OF VENOUS THROMBOEMBOLISM IN TRAUMA PATIENTS

The Virchow triad, which consists of blood stasis, endothelial injury, and hypercoagulability, broadly defines the factors that determine the propensity to form clot. Although trauma is a heterogeneous disease, any patient with penetrating trauma and many patients with blunt trauma will experience endothelial injury. The coagulation cascade will be activated at the site of injury, triggered by the exposure of the collagen matrix and basement membrane that support the endothelial lining. Endothelial damage in one area will cause systemic changes, and clot can form in areas far from the primary injury site, mainly the venous system in the lower extremities. The greater the overall damage to the endothelium, the higher is the propensity to form clot.¹

All patients with major trauma will experience stasis during their recovery period. As mentioned above, patients injured in a combat theater, for any given degree of injury, are more likely to require prolonged intubation, sedation, and paralysis because of the need for rapid air evacuation back to Germany and the continental United States. Although deep venous thrombosis (DVT) can occur within the first 24 hours after injury, rates increase significantly during recovery, reflecting the cumulative effect of longer time periods of immobility.²⁻⁴

Traumatic injury results in derangements of the coagulation cascade, including an increase in circulating tissue thromboplastin and activated procoagulants and a decrease in fibrinolytic activity. The resulting hyper-

coagulable state tends to be proportional to the degree of injury and decrease in tissue perfusion.¹ It follows that trauma patients who are not being adequately prophylaxed have high rates of DVT and pulmonary embolism (PE).

Effects of Massive Transfusion, Factor VIIa, and Tranexamic Acid

For research purposes, a massive transfusion is defined as the requirement for more than 10 units of packed red blood cells (pRBCs) during a resuscitation. Recent data from Operation Iraqi Freedom (OIF) shows that 5% of all patients admitted to US combat support hospitals in theater require a massive transfusion.⁵ Data from OIF has also shown that during resuscitation a 1:1 ratio of pRBCs to fresh frozen plasma (FFP) is associated with a lower mortality than higher ratios.⁵ The result has been a change in focus, where clinical practice guidelines for resuscitations in theater call for limiting crystalloid and increasing the use of whole blood, FFP, platelets, cryoprecipitate, and factor VIIa.

Because of the increases in inflammation, mortality, and multiorgan failure associated with massive transfusion, an increase in VTE among patients who survive their initial injury might be expected.⁶ In fact, the need for a massive transfusion is an independent predictor of delayed initiation of chemical prophylaxis, which subsequently increases the risk for VTE during

recovery.⁷ Transfusion of pRBCs has been independently associated with VTE in patients recovering from trauma.^{4,8,9} In a study of patients in medical and surgical intensive care units, platelet transfusion was independently associated with VTE, although this particular study excluded patients with traumatic injuries.¹⁰

Although the effects that FFP and cryoprecipitate have on multiple organ failure and lung injury have been well described,^{11,12} it is not clear whether either represents an independent risk factor for VTE. One small study found that receipt of FFP was highly associated with VTE, but the patients receiving FFP also received over 10 units of pRBCs, so an independent effect from FFP could not be established.⁹ Because military protocols have advocated fixed ratios of blood component products during resuscitation, it has been difficult to isolate the effect that any individual component has on VTE risk in the active duty population recovering from a combat injury.⁴

The CRASH-2 trial, a large randomized study of tranexamic acid use for trauma, did not show an increased risk of vascular occlusion, a composite secondary outcome measure that included pulmonary embolism.¹³ A randomized study of factor VIIa use for trauma patients also did not show an increased risk for thromboembolic events,¹⁴ although this study was much smaller than the CRASH-2 trial. Two studies of factor VIIa in US military casualties did not find an increase in thromboembolic events either.^{4,15} In a review of thromboembolic complications resulting from the use of factor VIIa at their institution, authors from the Baltimore Shock Trauma Center found DVT or PE in 6 of 285 patients (2.1%) who had received the drug. There was no comparison group available, and this VTE rate seems well within what would be expected in the typical trauma population who had not received factor VIIa.¹⁶

In summary, pRBCs and platelets have been independently associated with VTE in trauma and critically ill patients, respectively. Although FFP, cryoprecipitate, factor VIIa, and tranexamic acid have not been proven to increase VTE risk, given their mechanism of action and known effects on coagulation, it seems reasonable to assume they increase the likelihood for clot to some degree. A higher VTE rate during recovery

should be expected for patients who survive a massive transfusion.

Prevalence of Venous Thromboembolism in Trauma Patients

Early estimates put the rate of DVT in young patients with major trauma and without prophylaxis at approximately 20%; both elderly patients with a hip fracture and patients with head or spinal cord injury have an estimated rate of 40%.¹⁷ Likely due to the inherent heterogeneity of any trauma population studied, DVT rates in other reports vary from 20% to 90%.^{1,18} Patient inclusion criteria, imaging modalities used for surveillance and detection, and the presence of prophylaxis will significantly affect overall VTE rates. For similar reasons, PE rates also vary by report, ranging from 4% to 22%,¹ with some estimated rates as low as 0.7%.¹⁹

Walter Reed Army Medical Center (WRAMC; now Walter Reed National Military Medical Center), where a large proportion of combat casualties are ultimately transferred after being injured in theater, has collected data on VTE events among casualties from OIF and Operation Enduring Freedom (OEF). Over a period of 18 months, from September 2009 through March 2011, data on 506 patients was recorded. No systematic screening was performed, but 46 patients (9.1%) had a documented VTE, and 18 (39.1%) of these events occurred during the initial air evacuation prior to the patient being admitted to WRAMC.⁴

Data from clinical studies have identified specific risk factors that predispose patients to the development of VTE.^{1,8,20,21} The typical combat casualty requires surgery and central venous catheterization, which both increase the risk for VTE in all hospitalized patients.²⁰ In trauma patients specifically, the following factors have been independently associated with VTE in individual studies or metaanalyses: age, blood transfusion, surgery, lower extremity fracture,⁴ long bone fracture, spinal fracture, pelvic fracture, spinal cord injury, delay in initiating chemical prophylaxis, and increasing injury severity score (ISS).^{8,21} It is not clear at this time how each factor interacts with the others to provide a cumulative risk score for a given patient.

PREVENTION OF VENOUS THROMBOEMBOLISM

Chemical prophylaxis with unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) is the primary method of prophylaxis for most hospitalized patients.²⁰ Trauma patients, and especially those injured on the battlefield via high-velocity gunshots

or IEDs, pose a unique challenge because they can initially present with a hypocoagulable state. Given modern surgical techniques that involve damage control, packing of wounds, and early evacuation, physicians are often hesitant to start any therapy that might

increase the risk for bleeding. Therefore, this chapter will discuss mechanical methods of prophylaxis (the sequential compression device [SCD]) and prophylactic inferior vena cava (IVC) filters as alternatives to heparin for prophylaxis. Much of the discussion will be based on two major position papers, the Eastern Association for the Surgery of Trauma (EAST) guidelines for prevention of VTE in trauma patients, published in 2002,²¹ and the American College of Chest Physicians (ACCP) guidelines published in 2008 for prevention of VTE in all hospitalized patients.²⁰

Mechanical Prophylaxis

An SCD is a dynamic device that fits like a sleeve over an extremity, usually the calf or thigh, and provides intermittent compression generated by an external compressor. SCDs have been shown to affect two components of the Virchow triad. They reduce stasis by increasing blood flow in the extremity they are worn on, and they increase fibrinolysis, thereby reducing blood coagulation. Of note, both effects seem to decline rapidly once SCDs are removed, implying that continuous, uninterrupted use is required for optimal benefit.²¹

Studies assessing the efficacy of SCDs in hospitalized patients and in trauma patients in particular have been inconsistent. The EAST guidelines²¹ cite a lack of level I and II evidence, and use level III evidence to conclude there is no evidence that SCDs prevent VTE when compared to no prophylaxis. They note that there is some data to support the use of SCDs in head-injured patients. A recent metaanalysis of patients requiring neurosurgery would support this benefit, but the studies included in the analysis were not made up of trauma patients.²²

A metaanalysis published in 2006 also concluded that SCDs have no benefit over placebo. This analysis included only two randomized controlled trials (RCTs)²³ with a combined total of 562 trauma patients. Three other RCTs and 13 observational studies were reviewed, but methodological issues in each study and differences between studies prevented meaningful interpretation and pooling of the data.

The 2008 ACCP guidelines also note the lack of good evidence for efficacy. They discuss the additional concerns that up to a third of all trauma patients will have a contraindication to SCDs due to extremity injuries, and nursing and patient compliance with SCDs tends to be poor. In summary, they recommend the use of SCDs for all trauma patients with a contraindication to chemical prophylaxis.²⁰

The US military has adopted this approach for in-theater casualties,²⁴ which seems prudent for the

following reasons: (1) a significant number of patients injured in theater will have an initial contraindication to chemical prophylaxis; (2) there is physiologic data and rationale to support the use of SCDs; and (3) SCDs seem to have few side effects provided they are not applied to an injured extremity. In addition, in studies of critically ill or traumatically injured patients who were screened for events, 3% to 10% of patients who develop DVT have the clot detected on their initial, day 1 ultrasound.^{7,9,10,25} Delay in the initiation of chemical prophylaxis of more than 4 days from the date of injury results in three times the risk of VTE compared to institution of chemical prophylaxis within the first 48 hours.⁷ SCDs would seem a safe and potentially effective “bridge” to chemical prophylaxis to reduce this risk.

Unfortunately, many patients with IED injuries will not be able to use SCDs on their lower extremities. Although the data supporting the use of SCDs on the upper extremity for prevention of VTE is particularly weak,²¹ for the reasons listed above, this approach would also be reasonable for the high-risk trauma patient with no other options for prophylaxis.

Chemical Prophylaxis

Because several studies have shown that UFH may not be sufficient for prophylaxis in trauma patients, the EAST guidelines recommend LMWH be used. These guidelines list nine studies that evaluated the use of UFH for patients recovering from major trauma, including a metaanalysis showing no reduction in VTE events when UFH is used for prophylaxis.²⁶ Although the 9th consensus ACCP guidelines cite this same report, many of the studies suffer from small sample sizes, and they note the possibility of type II error.²⁷

LMWH has become the treatment of choice for high-risk trauma patients.^{20,21} This is mainly due to its safety and ease of use, and because a high-quality RCT showed superiority to UFH. Data from service members evacuated to WRAMC with traumatic injuries also show that LMWH specifically is associated with a reduced risk for VTE.⁴ The following discussion reviews the individual studies and consensus guidelines that recommend LMWH for trauma patients.

In a study of 442 trauma patients comparing a LMWH to a mechanical method of prophylaxis (SCD), only one patient in the group randomized to Lovenox (Sanofi, Bridgewater, NJ) 30 mg, subcutaneous, twice a day, suffered from DVT.²⁸ There was no significant increase in bleeding in the Lovenox group, implying that LMWH would not increase bleeding risk more than using SCD alone. However, the SCD group in this study also had a low rate of VTE that was not signifi-

cantly different than the LMWH group. Knudson²⁹ also compared Lovenox 30 mg, subcutaneous, twice a day, to mechanical prophylaxis and found no difference in VTE rates, although the number of events across both groups was very small. Knudson found no significant increase in bleeding in the LMWH group.

Stannard³⁰ compared two different prevention protocols using Lovenox 30 mg, subcutaneous, twice a day, in 200 orthopedic trauma patients. One group started Lovenox within 48 hours of admission, while the other started mechanical prophylaxis and delayed Lovenox for 5 days. For the entire population, 22 of 200 patients (11%) experienced DVT. There was no statistically significant difference between groups.

In a prospective cohort study of high-risk trauma patients (mean ISS = 19.5) receiving the LMWH dalteparin at a dose of 5,000 units daily, rates of DVT and PE were 3.9% and 0.8%, respectively. Of the 16 patient deaths, none was judged as being due to PE or late hemorrhage.³¹ In an RCT that enrolled orthopedic trauma patients and compared two different doses of the LMWH nadroparin, 3 of 215 patients (1.4%) had DVT after 10 days, and 5 of 150 (3.3%) had DVT after 6 weeks. Major hemorrhage occurred in 10 of 283 patients (3.5%).³²

In an RCT with 344 patients with trauma and an ISS greater than or equal to 9, Lovenox 30 mg twice a day was significantly more efficacious than UFH 5,000 units twice a day for reducing DVT.³³ LMWH was not associated with an increase in bleeding rates or blood transfusions when compared to UFH. Patients in this trial underwent surveillance and evaluation for symptoms with a combination of ultrasound and confirmatory venography. Patients in the LMWH group had 40 total (31%) and 8 proximal DVTs (6.2%), still a significant number.

Four other trials have compared UFH to LMWH.³⁴⁻³⁷ The three that were randomized found that there were fewer VTEs in the LMWH group, but only one found a statistically significant difference.³⁶ The average sample size for these trials was less than 50 patients. The fourth trial was a before-and-after comparison that was carried out after hospital protocol was switched from LMWH to UFH three times daily for trauma patients.³⁷ Among a total of 476 patients, no difference in VTE rates between the two regimens was found.

More recently, a small study of surgical intensive care unit patients, 85% of whom suffered from trauma, found that anti-Xa levels were subtherapeutic in 50% of patients receiving Lovenox 30 mg, subcutaneous, twice a day, for prophylaxis.³⁸ For the entire group, 26% had a VTE during their hospitalization, and those with subtherapeutic levels of anti-Xa were significantly more likely to experience a VTE. Given these findings, along

with the high rates of VTE for patients on LMWH in the Geerts,³³ Holley,⁴ and Stannard³⁰ studies, the search for a better chemical agent or method to prevent VTE in trauma patients continues.¹⁸ In the meantime, Lovenox 30 mg, subcutaneous, twice a day, has the most data to support safety and efficacy and should remain the agent of choice for prophylaxis for the trauma patient.

Neuraxial Blockade

Given the high doses of analgesic medications required for pain control in the multitrauma OEF/OIF patients and the known side effects of narcotics, early placement of epidural and peripheral nerve catheters (collectively referred to as neuraxial blockade [NAB]) is being recommended.³⁹ For those patients who receive an epidural or deep peripheral block, there is a small but real risk of hematoma. Outcomes after epidural or spinal hematoma are largely dependent on the speed with which the resulting neurologic deficits are recognized and the blood is surgically evacuated.⁴⁰ For the intubated, sedated, and often paralyzed combat casualty being flown across multiple time zones, new deficits can easily be missed.

It is clear that the presence of anticoagulation increases the risk for hematoma, though the consequences are much worse for epidural and deep peripheral blocks (at noncompressible sites).⁴⁰ Based on case reports published in the literature and adverse drug reports from LMWH manufacturers, risk factors for spinal hematoma in the presence of LMWH prophylaxis have been identified. LMWH twice per day was associated with an increased risk, as was the use of nonsteroidal antiinflammatory drugs or other anticoagulants in addition to LMWH prophylaxis. Because LMWH twice daily is the recommended treatment dose for trauma prophylaxis and aspirin is often used when a traumatic vascular injury requires grafting, neuraxial blockade can limit treatment options in the trauma patient. Only one study has specifically looked at the effect that extended periods of NAB have on VTE rates for hospitalized trauma patients.⁴¹ Though chemical prophylaxis was reduced in accordance with guidelines, there was no increase in VTE rates in the group receiving NAB.

Inferior Vena Cava Filters

The use of an IVC filter for VTE prophylaxis in the trauma patient is controversial. Both the ACCP and EAST guidelines acknowledge that there is no high quality evidence to support their use. A recent metaanalysis could not find any randomized trials to evaluate their use.⁴² According to the EAST guide-

lines, observational studies that compare outcomes to historical controls support the use of IVC filters as prophylaxis for the high-risk trauma patient with contraindications to chemical prophylaxis. The ACCP did not feel there was sufficient evidence to make such a recommendation. Although removable filters are discussed by both, neither feels that they alter the risk–benefit ratio sufficiently to change their general conclusions about prophylactic filter placement at this time.

The metaanalysis⁴² noted that of the observational studies assessed, only two recorded DVT as an outcome. Neither screened for DVT; they only recorded

symptomatic events. Although a statistically significant difference was not found, the number of events was small, and one study did show more DVTs in the filter group. The two observational studies did find a significant decrease in PEs favoring the prophylactic filter group. In their conclusions though, the meta-analysis authors note that because most of the studies were more than a decade old, they did not follow current guidelines for chemical VTE prophylaxis. If they had, it is not clear what the effect of prophylactic filter placement would have been. Therefore, the authors concluded that they could not recommend for or against their placement.

SUMMARY

Acute trauma patients have a high rate of VTE if prophylaxis is not instituted. The average combat casualty who is critically injured is at particularly high risk, and poses unique challenges. Chemical prophylaxis should be started as soon as it is considered safe to do so. Until it is safe, mechanical prophylaxis should be

used. A careful risk–benefit assessment must be done for each patient before NAB is started, but limited data in the combat-injured military population show that placement does not increase VTE rates. In the appropriate, high-risk patient with contraindications to chemical prophylaxis, an IVC filter could be considered.

REFERENCES

1. Shackford SR. Deep venous thrombosis and pulmonary embolism in trauma patients. *J Intensive Care Med.* 1988;3:87–98.
2. Coon WW. Risk factors in pulmonary embolism. *Surg Gynecol Obstet.* 1976;143:385–390.
3. Sevitt S, Gallagher N. Venous thrombosis and pulmonary embolism: a clinico-pathological study in injured and burned patients. *Br J Surg.* 1961;48:475–489.
4. Holley AB, Petteys S, Mitchell JD, Holley PR, Collen JF. Thromboprophylaxis and VTE rates in soldiers wounded in Operation Enduring Freedom and Operation Iraqi Freedom. *Chest.* 2013;144(3):966–973.
5. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma.* 2007;63:805–813.
6. Sihler KC, Napolitano LM. Complications of massive transfusion. *Chest.* 2010;137:209–220.
7. Nathens AB, McMurray MK, Cuschieri J, et al. The practice of venous thromboembolism prophylaxis in the major trauma patient. *J Trauma.* 2007;62:557–563.
8. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after trauma. *N Engl J Med.* 1994;331:1601–1606.
9. Knudson MM, Collins JA, Goodman SB, McCrory DW. Thromboembolism following multiple trauma. *J Trauma.* 1992;32:2–11.
10. Cook D, Crowther M, Meade M, et al. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Crit Care Med.* 2005;33:1565–1571.
11. Norda R, Tynell E, Akerblom O. Cumulative risks of early fresh frozen plasma, cryoprecipitate, and platelet transfusion in Europe. *J Trauma.* 2006;60:S41–S45.
12. MacLennan S, Williamson LM. Risks of fresh frozen plasma and platelets. *J Trauma.* 2006;60:S46–S50.

13. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376:23–32.
14. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*. 2005;59:8–18.
15. Wade CE, Eastridge BJ, Jones JA, et al. Use of recombinant factor VIIa in US military casualties for a five-year period. *J Trauma*. 2010;69:353–359.
16. Thomas GO, Dutton RP, Hemlock B, et al. Thromboembolic complications associated with factor VIIa administration. *J Trauma*. 2007;62:564–569.
17. Prevention of venous thrombosis and pulmonary embolism. NIH Consensus Development. *JAMA*. 1986;256:744–749.
18. Velmahos G. The current status of thromboprophylaxis after trauma: a story of confusion and uncertainty. *Am Surg*. 2006;72:757–763.
19. Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH. Deep venous thrombosis and its prevention in critically ill adults. *Arch Intern Med*. 2001;161:1268–1279.
20. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:381S–453S.
21. Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. *J Trauma*. 2002;53:142–164.
22. Collen JF, Jackson JL, Shorr AF, Moores LK. Prevention of venous thromboembolism in neurosurgery: a metaanalysis. *Chest*. 2008;134:237–249.
23. Limpus A, Chaboyer W, McDonald E, Thalib L. Mechanical thromboprophylaxis in critically ill patients: a systematic review and meta-analysis. *Am J Crit Care*. 2006;15:402–412.
24. US Army Medical Department, Institute of Surgical Research. *The Prevention of Deep Venous Thrombosis—IVC Filter*. Fort Sam Houston, TX: ISR; 2012. Joint Theater Trauma System Clinical Practice Guideline. http://www.usaisr.amedd.army.mil/assets/cpgs/Prevention_of_Deep_Venous_Thrombosis_24_Apr_12.pdf. Accessed November 19, 2013.
25. Velmahos GC, Nigro J, Tatevossian R, et al. Inability of an aggressive policy of thromboprophylaxis to prevent deep venous thrombosis (DVT) in critically injured patients: are current methods of prophylaxis insufficient? *J Am Coll Surg*. 1998;187:529–533.
26. Velmahos GC, Kern J, Chan L, Oder D, Murray JA, Shekelle P. Prevention of venous thromboembolism after injury: an evidence-based report—part I: analysis of risk factors and evaluation of the role of vena cava filters. *J Trauma*. 2000;49:132–139.
27. Gould M, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e227S–e277S.
28. Ginzburg E, Cohn SM, Lopez J, et al. Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *Br J Surg*. 2003;90:1338–1344.
29. Knudson MM, Morabito D, Paiement GD, Shckleford S. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. *J Trauma*. 1996;41:446–459.
30. Stannard JP, Lopez-Ben RR, Volgas DA, et al. Prophylaxis against deep-vein thrombosis following trauma: a prospective, randomized comparison of mechanical and pharmacologic prophylaxis. *J Bone Joint Surg Am*. 2006;88:261–266.

31. Cothren CC, Smith WR, Moore EE, Morgan SJ. Utility of once-daily dose of low-molecular weight heparin to prevent venous thromboembolism in multisystem trauma patients. *World J Surg.* 2007;31:98–104.
32. Haentjens P. Thromboembolic prophylaxis in orthopaedic trauma patients: a comparison between a fixed dose and an individually adjusted dose of a low molecular weight heparin (nadroparin calcium). *Injury.* 1996;27:385–390.
33. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med.* 1996;335:701–707.
34. Cohn SM, Feinstein AJ, Burns GA, Ginzburg E, Hammers LW. Prospective trial of low-molecular-weight heparin versus unfractionated heparin in moderately injured patients. *Vasc Endovasc Surg.* 1999;33:219–223.
35. Greenfield LJ, Proctor MC, Rodriguez JL, Luchette FA, Cipolle MD, Cho J. Posttrauma thromboembolism prophylaxis. *J Trauma.* 1997;42:100–103.
36. Green D, Lee MY, Lim AC, et al. Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. *Ann Intern Med.* 1990;113:571–574.
37. Arnold JD, Dart BW, Barker DE, et al. Gold Medal Forum Winner. Unfractionated heparin three times a day versus enoxaparin in the prevention of deep venous thrombosis in trauma patients. *Am Surg.* 2010;76:563–570.
38. Malinoski D, Jafari F, Ewing T, et al. Standard prophylactic enoxaparin dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients. *J Trauma.* 2010;68:874–880.
39. US Army Medical Department, Institute of Surgical Research. *Management of Pain, Anxiety, and Delirium in Injured Warfighters.* Fort Sam Houston, TX: ISR; 2010. Joint Theater Trauma System Clinical Practice Guideline. http://www.usaisr.amedd.army.mil/assets/cpgs/Management_of_Pain_Anxiety_and%20Delirium_5_Apr_2013.pdf. Accessed November 19, 2013.
40. Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (The second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med.* 2003;28:172–197.
41. Holley AB1, Petteys S, Mitchell JD, et al. Venous thromboembolism prophylaxis for patients receiving regional anesthesia following injury in Iraq and Afghanistan. *J Trauma Acute Care Surg.* 2014;76(1):152–159.
42. Rajasekhar A, Lottenberg R, Lottenberg L, Liu H, Ang D. Pulmonary embolism prophylaxis with inferior vena cava filters in trauma patients: a systematic review using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines. *J Thromb Thrombolysis.* 2011;32:40–46.