American Association for the Surgery of Trauma/American College of Surgeons-Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma

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David G. Jacobs, UpToDate, Royalties, Authorship; Lena Napolitano, Merck Global Negative Advisory Board/Abbvie Critical Care Working Group, Consulting fee, Advisor/Consultant. Brian K. Yorkgitis, Allison E. Berndtson, Alisa Cross, Ryan Kennedy, Matthew P. Kochuba, Christopher Tignanelli, Gail T. Tominaga, William H. Marx, Dennis W. Ashley, Eric J. Ley, Todd W. Costantini have nothing to disclose.

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Brian K. Yorkgitis, PA-C, DO, FACS, Allison E. Berndtson, MD, FACS, Alisa Cross, MD, Ryan Kennedy, MD, FACS, Matthew P. Kochuba, MD, Christopher Tignanelli, MD, MS, FACS, Gail T. Tominaga, MD, FACS, David G. Jacobs, MD, FACS, William H. Marx, DO, FACS, Dennis W. Ashley, MD, FACS, Eric J. Ley, MD, Lena Napolitano, MD, FACS, FCCP, FCCM, *and* **Todd W. Costantini, MD, FACS**, *San Diego, California*

ABSTRACT: Trauma patients are at increased risk of venous thromboembolism (VTE), which includes both deep vein thrombosis and pulmonary embolism. Pharmacologic VTE prophylaxis is a critical component of optimal trauma care that significantly decreases VTE risk. Optimal VTE prophylaxis protocols must manage the risk of VTE with the competing risk of hemorrhage in patients following significant trauma. Currently, there is variability in VTE prophylaxis protocols across trauma centers. In an attempt to optimize VTE prophylaxis for the injured patient, stakeholders from the American Association for the Surgery of Trauma and the American College of Surgeons-Committee on Trauma collaborated to develop a group of consensus recommendations as a resource for trauma centers. The primary goal of these recommendations is to help standardize VTE prophylaxis strategies for adult trauma patients (age ≥15 years) across all trauma centers. This clinical protocol has been developed to (1) provide standardized medication dosing for VTE prophylaxis in the injured patient; and (2) promote evidence-based, prompt VTE prophylaxis in common, high-risk traumatic injuries. (*J Trauma Acute Care Surg.* 2022;92: 597–604. Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level V.
KEY WORDS: Deep vein thrombosis; pulmonary embolism; enoxaparin; heparin; ultrasound.

Trauma patients are at increased risk for venous thromboembolism (VTE), comprised of pulmonary embolism (PE) and deep venous thrombosis (DVT). Venous thromboembolism impacts an estimated 900,000 people in the United States each year and results in several hundred thousand hospitalizations and approximately 60,000 to 100,000 deaths.[1] Approximately two-thirds of VTE episodes manifest as DVT and one-third as PE with or without DVT.[2,3] Trauma is a known risk factor for VTE which is thought to be secondary to decreased venous blood flow, diminished fibrinolysis, immobilization, release or exposure of tissue factor, and depletion of endogenous anticoagulants, such as antithrombin.[4] The incidence of DVT in trauma patients has a range of 5% to 63%, depending on patient risk factors, modality of prophylaxis, and methods of detection. It is clear that VTE accounts for significant morbidity and mortality in the injured patient.[5–11]

While elevated risk of VTE for patients posttrauma is widely recognized, there remains significant variability in clinical practice related to timing of initiation of pharmacologic prophylaxis, as well as selection of the specific chemoprophylaxis agent.[12–15] Not only is there significant inconsistency in practice between centers but also controversy regarding optimal VTE prophylaxis strategies between the trauma provider and the surgical specialists that are involved in the multidisciplinary care of trauma patients is common. This variability in practice related to VTE prophylaxis timing and dosing extends to orthopedic surgeons, spine surgeons, and neurosurgeons, making consensus between providers challenging.[16–19]

PROTOCOL RATIONALE AND GOALS

While there are many algorithms and guidelines produced with the goal of reducing VTE in trauma patients (Table 1), institutional protocols for pharmacologic VTE prophylaxis differ across trauma centers in the United States.[20–22] Further, optimal VTE prophylaxis strategies for high-risk trauma patients with competing risks of hemorrhage and the need for aggressive pharmacologic prophylaxis because of increased VTE risk represent a challenge for the multidisciplinary trauma team. The primary goal of these recommendations is to help standardize VTE prophylaxis strategies for adult trauma patients (age ≥15 years) across all trauma centers.

The goal of this clinical protocol is to (1) provide standardized medication dosing for VTE prophylaxis in the injured patient; (2) promote evidence-based, prompt VTE prophylaxis in common, high-risk traumatic injuries; and (3) review interventions that are utilized with significant variability in trauma centers, including inferior vena cava filters (IVCFs) and routine lower-extremity screening venous duplex. We have developed a

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From the Division of Acute Care Surgery, Department of Surgery (B.K.Y., M.P.K.), University of Florida-Jacksonville, Jacksonville, Florida; Division of Trauma Surgical Critical Care, Burns and Acute Care Surgery, Department of Surgery (A.E.B., T.W.C.), UC San Diego School of Medicine, San Diego, California; Department of Surgery (A.C., R.K.), University of Oklahoma Health Science Center, Oklahoma City, Oklahoma; Department of Surgery (C.T.), University of Minnesota, Minneapolis, Minnesota; Trauma Services (G.T.T.), Scripps Memorial Hospital La Jolla, La Jolla, California; Division of Acute Care Surgery/Department of Surgery (D.G.J.), Atrium Health-Carolinas Medical Center, Charlotte, North Carolina; Division of Trauma and Acute Care Surgery (W.H.M.), Upstate Medical University, Syracuse, New York; Department of Surgery (D.W.A.), Mercer University School of Medicine, Atrium Health Navicent, Macon, Georgia; Department of Surgery (E.J.L.), Cedars-Sinai Medical Center, Los Angeles, California; and Trauma and Surgical Critical Care, Department of Surgery (L.N.), University of Michigan Health System, Ann Arbor, Michigan.
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Address for reprints: Todd W. Costantini, MD, FACS, Division of Trauma, Surgical Critical Care, Burns and Acute Care Surgery, Department of Surgery, UC San Diego School of Medicine 200 W. Arbor Drive #8896 San Diego, CA 92103 619-543-7200; email: tcostantini@health.ucsd.edu.

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TABLE 1. National and International VTE Guidelines

Society	Guidelines	Citations
Western Trauma Association	Updated guidelines to reduce VTE in trauma patients: A Western Trauma Association critical decisions algorithm.	Ley et al. J Trauma Acute Care Surg. 2020:89:971–981.
American Association for the Surgery Critical Care Committee	VTE prophylaxis in the trauma intensive care unit: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document	Rappold et al. Trauma Surgery & Acute Care Open. 2021;6:e000643.
Eastern Association for the Surgery of Trauma	Practice management guidelines for the prevention of VTE in Trauma Patients: The EAST practice management guidelines workgroup.	Rogers et al. J Trauma. 2002;53:142–164.
American College of Surgeons- Committee on Trauma	ACS TQIP Best Practices in the Management of TBI, January 2015.	https://www.facs.org/-/media/files/quality-programs/trauma/tqip/tbi_guidelines.ashx
American College of Chest Physicians	Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.	Guyatt et al. Chest. 2012;141:Suppl:7S–47S.
National Institute for Health and Care Excellence	NICE guidelines: VTE in over 16 s: reducing the risk of hospital-acquired DVT or PE, 2018.	https://www.nice.org.uk/guidance/ng89
American Society of Hematology	American Society of Hematology 2019 guidelines for management of VTE: Prevention of VTE in surgical hospitalized patients.	Blood Adv. 2019:3:3898–3944

consensus clinical pathway for VTE prophylaxis (Fig. 1) that can be implemented widely at all trauma centers.

This clinical protocol was developed by stakeholders from the American Association for the Surgery of Trauma and the American College of Surgeons—Committee on Trauma. A literature review was conducted by members of the work group to identify prospective and retrospective studies related to prophylaxis against DVT and/or PE in trauma patients. These studies were reviewed by members of the group, and consensus guidelines were generated based on current literature and expert opinion. Therefore, the clinical protocol presented here is based on best available evidence and the consensus of experts on this panel. However, treatment decisions regarding VTE prophylaxis should be individualized for each patient and do not exclude other treatment strategies as being within the standard of care. Ultimately, the responsibility to implement treatment decisions rest with the treating physician and not with the working group that has developed the protocol presented here.

Evidence Base: Brief Summary

VTE Risk Scoring Systems

Multiple scoring systems exist to stratify VTE risk and the need for pharmacologic prophylaxis. The Trauma Embolic Scoring System was developed specifically for trauma patients and includes obesity, ventilator duration longer than 3 days, lower-extremity trauma, age, and Injury Severity Score as risk factors for VTE.[23] A Trauma Embolic Scoring System score greater than 6 has a sensitivity of 81.6% and specificity of 84% for predicting VTE. In addition, the Risk Assessment Profile of Greenfield has been examined in trauma patients. Applying this scoring tool in a trauma population was found to have a sensitivity of 82% and

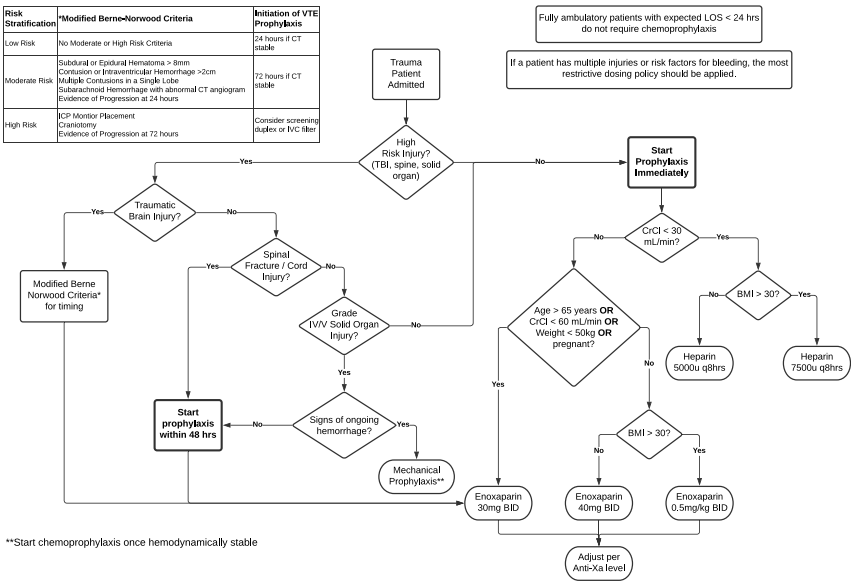

Figure 1. Inpatient trauma VTE prophylaxis algorithm.

specificity of 57% for predicting VTE.[24] Certain injury patterns are also known to be high risk for VTE development, including spine fracture, pelvic fracture, long bone fracture, and venous injury repair.[8] Further, comorbidities, including history of prior VTE, inherited clotting disorder, or the presence of malignancy should be considered when assessing VTE risk after trauma. While scoring systems are helpful for stratifying risk, most injured patients that require hospitalization are at increased risk of VTE. Therefore, we recommend that pharmacologic VTE prophylaxis should be initiated promptly, without the need for formal risk scoring, unless the patient is ambulatory and has an expected length of stay less than 24 hours.

Dosing of Pharmacologic VTE Prophylaxis

Enoxaparin is the first choice for pharmacologic VTE prophylaxis for trauma patients with higher doses now considered the standard of care. When choosing the starting dose, enoxaparin 40 mg twice daily should be initiated for most trauma patients as 30 mg twice daily may result in inadequate pharmacologic prophylaxis and a higher VTE rate.[25–29] Determining which patients should be started on a dose less than 40 mg twice daily may be based on age, weight, or creatinine clearance.[27] Patients who are older than 65 years, weigh less than 50 kg, or have a creatinine clearance of 30 to 60 mL/min should receive an initial enoxaparin dose of 30 mg twice daily because these characteristics are predictive of lower enoxaparin requirements.[22] Those with traumatic brain injury (TBI), spinal cord injury (SCI), and pregnant patients should also continue to receive an initial enoxaparin dose of 30 mg twice daily because of the need for additional research on enoxaparin dosing in these patients.[22] Mild to moderate thrombocytopenia (platelets, 50,000–100,000) should not interfere with VTE chemoprophylaxis.

After the initial enoxaparin dosing, adjustments may be needed to the dose according to anti-Xa levels, with a recommended target of 0.2 to 0.4 IU/mL for peak levels or 0.1 to 0.2 IU/mL for trough levels.[22,25–27] Increasing the initial enoxaparin dose for obesity may be considered although monitoring anti-Xa levels is recommended for the obese because of the fluctuations in creatinine clearance that may occur after trauma.[30] For patients with a body mass index greater than 30, enoxaparin may be dosed at 0.5 mg/kg twice daily.[29] Importantly, weight is not a significant predictor of which patients require a high or low enoxaparin dose, rather the creatinine clearance is the only independent factor that predicts the dose in high and low weight patients.[31,32] Care should be taken when dosing enoxaparin by weight in middle age or elderly obese trauma patients who have a low to normal creatinine clearance and, therefore, may require less than the predicted enoxaparin dose.[31] Similarly, young thin trauma patients with a high creatinine clearance may require a higher than predicted enoxaparin dose.[32] Whatever the dose, pharmacologic prophylaxis should be provided early and continuously for most trauma patients while avoiding missed doses for orthopedic and other surgical procedures.[22] For patients with end-stage renal disease or a creatinine clearance of less than 30 mL/min, subcutaneous unfractionated heparin (UH) at 5000 units every 8 hours is the preferred pharmacologic VTE prophylaxis.[22,33] For obese patients (body mass index > 30), UH may be dosed at 7500 units every 8 hours.[34] Other than for renal failure or a low creatinine clearance, enoxaparin is preferable to UH as enoxaparin has increased bioavailability, longer plasma-half life, more predictable pharmacokinetics and pharmacodynamics, interacts less with platelets, and an exceedingly rare incidence of heparin-induced thrombocytopenia at prophylactic dosing.[35,36] Although UH at 5000 units three times daily is often suggested as "noninferior" to enoxaparin 30 mg twice daily, enoxaparin is now provided at higher doses, so this comparison is no longer applicable to the current standard of care. In addition, support for UH three times daily is based on a trial that was underpowered to make this conclusion, and more recently, enoxaparin 30 mg twice daily was established as superior to UH 5000 units three times daily.[15,37,38]

VTE Pharmacologic Prophylaxis for Blunt Solid Organ Injury

Trauma patients with blunt solid organ injury have been shown to have a hypercoagulable phenotype as early as 12 hours from admission. Early pharmacologic VTE prophylaxis (≤48 hours) in patients with blunt solid organ injury has been associated with decreased DVT and PE rates without increased risk of failure of nonoperative management, transfusion requirements, or mortality in patients with moderate grades of AAST blunt solid organ injury.[39,40]

Early VTE prophylaxis (≤48 hours) was associated with decreased DVT (1.9% vs. 4.1%) and PE (1.0% vs. 1.8%) rates compared with late prophylaxis (>48 hours) in a study of 36,187 patients with blunt solid organ injury undergoing nonoperative management.[40] Patients in the late prophylaxis and no prophylaxis groups were more likely to have a high-grade blunt solid organ injury. There was no difference in failure of nonoperative management or postprophylaxis administration of packed red blood cell transfusion. Early VTE prophylaxis (≤48 hours) was associated with decreased DVT (3% vs. 9%) rates in another prospective study of 118 patients with blunt solid organ injury selected for nonoperative management.[41] There were no nonoperative failures or need for interventional radiology procedures after chemical VTE prophylaxis initiation. Patients in the late prophylaxis group were more likely to have a TBI.

Thus, we recommend early pharmacologic VTE prophylaxis (within 24–48 hours) in patients with blunt solid organ injury. Early pharmacologic VTE prophylaxis in Grade IV and Grade V injuries should be approached with caution as the literature regarding these grades of injury is sparse; however, pharmacologic VTE prophylaxis should be initiated once bleeding has stabilized.

VTE Pharmacologic Prophylaxis for TBI

Because of the potential for expansion of intracranial hemorrhage, TBI represents a special consideration for initiation of VTE prophylaxis following trauma. Approximately 54% to 63% of patients with TBI will develop a VTE if they do not receive appropriate chemical prophylaxis.[8,42] The most important finding when determining initiation of VTE chemical prophylaxis is progression of intracranial hemorrhage on imaging.[43] Utilization of the modified Berne-Norwood criteria, a tiered approach to guide VTE chemoprophylaxis initiation in patients with TBI has shown efficacy in VTE prevention and safety

TABLE 2. Modified Berne-Norwood Criteria[44]

Risk Stratification	Criteria	Initiation of VTE Prophylaxis
Low risk	No moderate- or high-risk criteria	Pharmacologic prophylaxis at 24 h if CT stable
Moderate risk	Subdural hematoma >8 mm Epidural hematoma >8 mm Contusion or intraventricular hemorrhage >2 cm Multiple contusions in a single lobe Subarachnoid hemorrhage with abnormal CT angiogram Evidence of progression at 24 h	Pharmacologic prophylaxis at 72 h if CT stable
High risk	ICP monitor placement Craniotomy Evidence of progression at 72 h	Consider screening lower-extremity duplex or IVC filter

(Table 2). These criteria risk stratify patients into low, medium and high-risk TBIs. The importance of treating TBI as a heterogeneous disease aligns with clinical practice where increased severity of intracranial hemorrhage is associated with significantly higher rates of TBI progression.[44–49] Patients with low-risk TBI without progression on follow-up CT scan may have prophylaxis safely initiated at 24 hours postinjury. Patients with high-risk TBI without progression on repeat imaging can have VTE prophylaxis safely initiated at 72 hours.[50] Adherence with the modified Berne-Norwood criteria is associated with a significant reduction in VTE events for TBI patients without added risk of TBI progression.[44,51,52]

Many trauma centers follow the Brain Injury Guidelines (BIG) in which repeat CT head is not routinely done in BIG 1 and 2 injuries and is done at 6 hours after the initial head CT in BIG 3 patients.[53] Initiation of VTE chemical prophylaxis in the low-risk BIG 1 and 2 may be prudent 24 hours to 48 hours after injury if neurologic examination remains stable. In patients in the BIG 3 category, initiation should be considered in less than 72 hours if the patient remains stable on neurologic examination and has no expansion of intracranial hemorrhage on repeat imaging.[52]

VTE Pharmacologic Prophylaxis for Spinal Fracture/SCI

Patients with spine fracture and/or SCI are at very high risk for the development of VTE complications.[8] The primary risk factor in SCI appears to be the venous stasis associated with the loss of voluntary motor function in this patient population. Thus, initiation of chemoprophylaxis as soon as possible following injury is necessary to reduce morbidity and mortality following SCI. However, similar to the TBI patient population, the hemorrhagic complications associated with chemoprophylaxis can be devastating, particularly in patients with SCI involving the cervical levels of the spinal cord.[54] For these reasons, determining the optimal timing of initiation of chemoprophylaxis following SCI or spinal fracture is of paramount importance, but is also somewhat controversial. While the overall strength of scientific evidence is low, it appears that initiation of pharmacologic VTE prophylaxis within 48 hours of injury or spine surgery is associated with a reduced incidence of DVT and PE, with no associated increase in hemorrhagic complications.[55–57]

An early observational study noted a lower incidence of VTE in patients given chemoprophylaxis within 72 hours of injury, but did not comment on the risk of hemorrhage complications.[58] Two more recent studies, both using a propensity-matched analysis of TQIP data, demonstrated a lower incidence of thromboembolic complications with no increase in hemorrhagic complications in patients started on low molecular weight heparin within 48 hours of injury or surgery, compared with those initiated after 48 hours. These patient populations included those with nonoperative blunt spine trauma without SCI, as well as patients with spine trauma managed operatively, with and without SCI.[59,60]

Intraspinal hematoma expansion is a particularly feared complication associated with early initiation of chemoprophylaxis in SCI patients. A recent single-institution retrospective study compared early (≤48 hours) versus late (>48 hours) initiation of chemoprophylaxis (heparinoids or aspirin), and noted only a 1% incidence of intraspinal hematoma expansion, with no significant difference in this complication between the early and late groups.[55] Thus, we recommend initiation of chemoprophylaxis within 48 hours of injury or spine surgery, as this strategy appears to be both effective in reducing the incidence of VTE in patients with spine fracture/SCI, and safe with respect to hemorrhagic complications, including intraspinal hematoma.

Screening Venous Duplex for DVT

There are wide variations in the practice of routine duplex ultrasonography to detect asymptomatic DVT in trauma centers.[61] Screening for DVT via lower-extremity ultrasonography (LUS) is associated with increased rate of detection for DVT, however is not associated with decreased PE rates.[62] A review of 442,108 patients from the National Trauma Data Bank evaluated the association between LUS and VTE diagnosis.[63] Centers were subgrouped as high screening (>2% of patients receiving LUS) and low screening (<2% of patients receiving LUS). The DVT identification was associated with high-screening centers (odds ratio, 1.43); however, there were no difference in PE rates (odds ratio, 1.01). Similarly, routine screening for DVT in asymptomatic trauma patients increases rate of VTE identification, however this does not appear to have an effect on rates of symptomatic VTE or PE. Routine VTE Screening is, therefore, not recommended for all trauma patients, and is a Grade 2C American College of Chest Physicians (CHEST) guideline.[33]

Routine screening for DVT in high-risk (Risk Assessment Profile >10), asymptomatic trauma patients may improve VTE identification and decrease rate of symptomatic PE. In addition, screening duplex for asymptomatic patients may identify thrombus with high-risk features that may be associated with elevated risk of PE. In a study of routine surveillance, a lower symptomatic

PE rate (1.9 vs. 7%) was reported in high-risk patients who were screened with weekly venous duplex ultrasound.[64] Caution should be applied as there was no standardization of timing of treatment postidentification of VTE, the overall number of PEs was low (3.7% of patients), and asymptomatic PEs that were identified were excluded. We recommend routine lower extremity duplex screening for asymptomatic patients only if they are considered high risk for VTE.

IVCF Placement

Current literature does not support the use of prophylactic IVCFs in trauma patients, based on data from a multicenter RCT of 240 patients with Injury Severity Score greater than 15, confirming no reduction in PE or 90-day mortality.[65] Early data before timelier and more aggressive pharmacologic VTE prophylaxis had shown utility to prophylactic IVCFs.[21] CHEST, the Society of Interventional Radiology and American Society of Hematology (ASH) all concluded that IVCFs should not be routinely used for VTE prophylaxis in trauma patients.[20,66,67]

The use of IVCFs is associated with an increased risk of DVT and low retrieval rate without a reduction in PE or mortality. Costs associated with IVCFs are not inconsequential.[68,69] In rare instances in which a trauma patient is at extremely high risk of complication from VTE chemoprophylaxis for a prolonged period, the risks and benefits of IVCF placement must be considered.[70] If IVCF placement is performed, structured follow-up programs are needed to resume anticoagulation when safe, and to increase IVCF retrieval rates and detect complications.[66,67,70]

Limitations

It is important to note that not all occurrences of VTE after trauma are preventable. In trauma patients, PE frequently occurs in the absence of DVT and is thought to originate de novo in the lungs as a result of activated pulmonary endothelium.[71] The decision to initiate VTE prophylaxis requires an analysis of the benefit of pharmacologic prophylaxis to decrease thrombosis versus the risk of bleeding in patients with high-risk injury patterns. These decisions must be individualized for each patient; however, all attempts should be made to initiate pharmacologic prophylaxis as soon as possible due to the high risk of VTE in the injured patient. While an extensive literature review was conducted and current studies were evaluated and discussed by work group members, a formal evaluation of the level of evidence reviewed nor the strength of recommendations provided are included as part of this clinical guideline. Finally, this clinical protocol provides recommendations for inpatient VTE prophylaxis but does not address the need for continued VTE prophylaxis after hospital discharge for high-risk patients with prolonged immobility, weight-bearing restrictions, or an ongoing prothrombotic state after injury.

CONCLUSION

With the inherent increased risk of VTE in the trauma population, prophylaxis remains paramount to prevent potentially lethal complications. Through this evidenced-based guideline, common areas of controversy with regards to VTE prophylaxis are addressed (see Supplemental Digital Content, http://links.lww.com/TA/C217). With varied VTE prophylaxis regimens throughout trauma centers, this clinical protocol provides recommendations to assist in standardizing VTE prophylaxis practices to minimize the risk of VTE in the injured patient. This clinical protocol can potentially serve as a resource for centers that currently do not have a formalized protocol for VTE prophylaxis or for centers that need to update their protocols to reflect more recent published data on optimal strategies.

AUTHORSHIP

All authors participated in the literature review and development of the clinical protocol. A.E.B., A.C. and R.K. developed the algorithm. B.K.Y., L.N., and T.W.C. drafted the article. All authors participated in critical review and revision of the article.

DISCLOSURE

The authors declare no conflicts of interest.

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