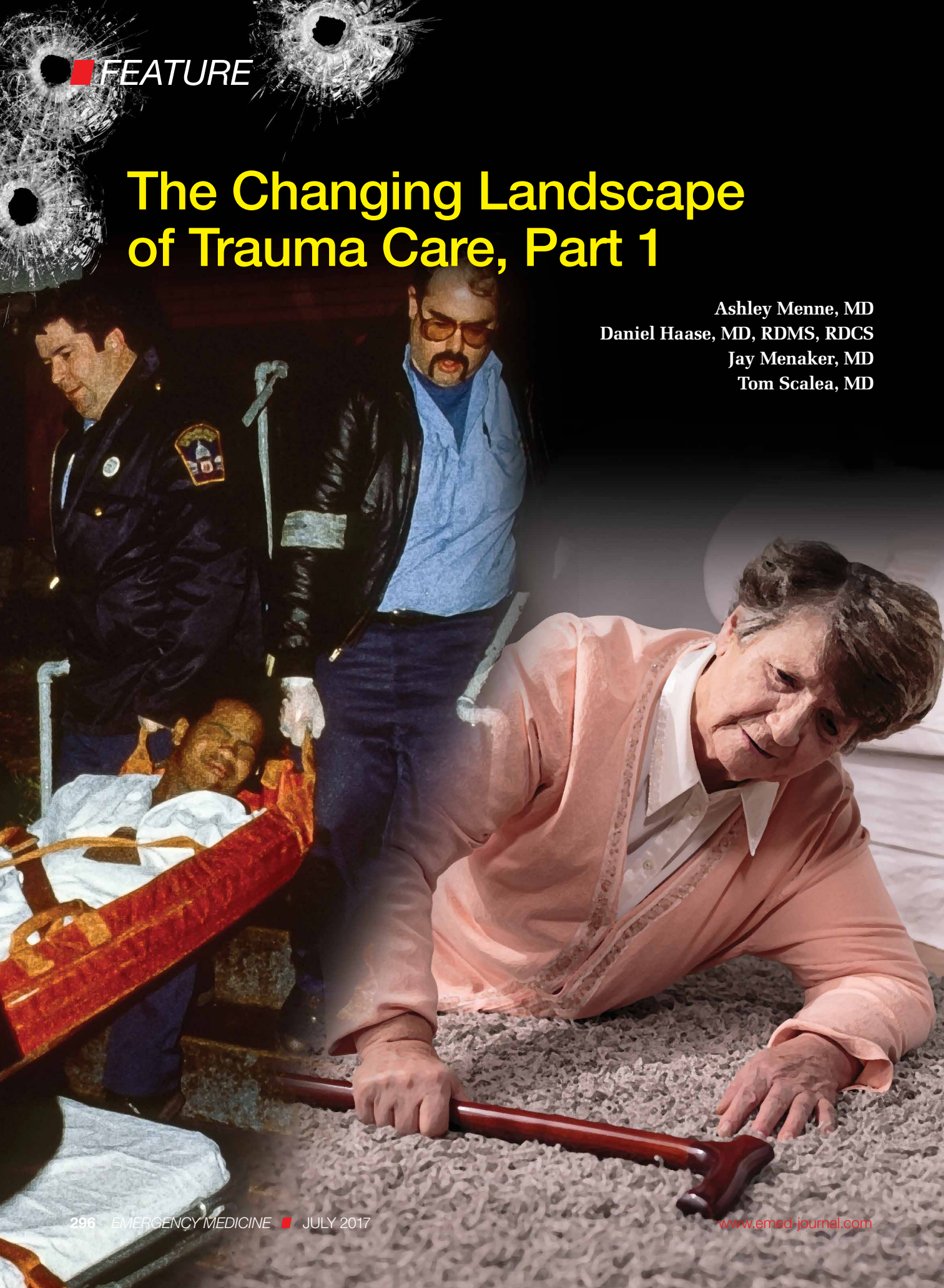
The Changing Landscape of Trauma Care, Part 1

Ashley Menne, MD
Daniel Haase, MD, RDMS, RDCS
Jay Menaker, MD
Tom Scalea, MD



In the first of two parts, the authors present the challenges in treating the increasing numbers of older trauma patients, patients on anticoagulation therapy, and patients with penetrating wounds.

Introduction

There has been a fundamental change in the face of injury in the United States. Traditionally, injury was thought to be a disease of the young male population, with motor vehicle collision (MVC) being the most common mechanism of injury. Depending on the trauma center, blunt trauma would comprise up to 99% of patients admitted. This profile has fundamentally changed over the last 15 years. Trauma center performance is often benchmarked against local, regional, or national norms, and as all medical centers now measure quality as the primary endpoint, these changes in demographics can be very important.

Certainly, the most important change has been the "graying" of trauma patients. When I (TS) started working in Baltimore 20 years ago, patients over age 65 years comprised approximately 5% of our total trauma admissions. Last year, over 30% of our 7,000 primary admissions were patients over age 65 years who had sustained ground-level falls.

Injury patterns in the elderly differ compared to standard blunt trauma in which traumatic brain injury (TBI) is common. Extremity fractures, particularly hip fractures, are common, whereas torso injuries other than rib fractures are relatively uncommon. As this article points out, elderly trauma patients almost universally have significant medical problems. Cognitive deficits and balance issues may explain ground-level falls in this population. Syncope from a myriad of underlying medical conditions and/or medications may have contributed to their falls as well.

The evaluation process for elderly trauma patients must be directed not only at diagnosing injury but also at attempting to identify the reason for the injury. This may involve a number of diagnostic tests in the ED, in the outpatient setting, or even on an inpatient floor.

Unfortunately, elderly patients can succumb to relatively minor injuries, and those who survive such afflictions often have difficulty making a full recovery. Many elderly patients who were able to function preinjury were marginally compensated at home. Operative therapy, often needed to treat injuries such as a hip or extremity fracture, by itself represents physiological burden to an elderly patient. Likewise, full recovery after even a mild TBI can be quite difficult.

Admitting an elderly patient to the hospital can present several challenges. For example, elderly patients are often on a number of prescription and nonprescription medications, including over-the-counter

Dr Menne is an assistant professor, department of emergency medicine, University of Maryland School of Medicine, Baltimore. **Dr Haase** is an assistant professor, department of emergency medicine, University of Maryland School of Medicine, Baltimore. **Dr Menaker** is a professor, department of surgery and emergency medicine; and the medical director, Lung Resuscitation Unit and Critical Care Resuscitation Unit, University of Maryland School of Medicine, Baltimore. **Dr Scalea** is Francis X Kelly distinguished professor of trauma, University of Maryland School of Medicine and Physician in Chief, R Adams Cowley Shock Trauma Center, Baltimore.

Authors' Disclosure Statement: The authors report no actual or potential conflict of interest in relation to this article.

DOI: 10.12788/emed.2017.0041

The evaluation process for elderly trauma patients must be directed not only at diagnosing injury but also at attempting to identify the reason for the injury.

nutritional and herbal supplements, many of which interact with the newly prescribed medications given to treat trauma (eg, analgesics, sedatives, antiseizure drugs). Moreover, elderly patients often become disoriented and agitated when they are out of their home environment. All too often, the therapy for these and other problems is another medication, and thus the cycle continues. Therefore, elderly patients are ultimately at increased risk for death from seemingly trivial injury, which in turn may create significant perceived quality issues for a medical center.

The use of systemic anticoagulation has become almost ubiquitous in older patients. Some days it seems like every patient I (TS) admit is taking an anticoagulant—at least aspirin. While primary care providers (PCPs) correctly realize the important role these anticoagulants have in treating chronic medical conditions, they often do not recognize the dangers associated with increased traumatic bleeding following an injury.

Frequently, we knowingly take patients with conditions such as rate-controlled atrial fibrillation (AF) off their prescribed anticoagulant, believing they are simply not candidates for anticoagulation because of their propensity to fall. Even though we attempt to communicate our concerns to the PCP, when these patients are readmitted, it is common to find that they have been placed back on an anticoagulant.

The advent of novel oral anticoagulants (NOACs) has made routine laboratory testing obsolete. One need only to turn on the television to see the many advertisements explaining why this agent or that agent is preferable to warfarin. While, fresh frozen plasma (FFP) and/or prothrombin complex concentrates (PCC) are quite effective at reversing the anticoagulant effect of warfarin, reversal of these newer agents is either extremely difficult or impossible.

Anticoagulant reversal can be more or less important, depending on the situation. For instance, while subcutaneous bleeding is concerning, it can be temporized by operative exploration and/or packing. When necessary, blood can be transfused to replace the blood lost. However, the same is not true for a patient with significant TBI, because even a small volume of ongoing hemorrhage can prove lethal. Cavitary hemorrhage in the chest and/or abdomen is also extremely difficult to treat if the anticoagulant effect cannot be reversed. Given the popularity of the new anticoagulants, I (TS) am afraid that this problem will be with us for years to come.

There has been a significant spike in interpersonal violence in the United States over the past few years. While the cause is often difficult to identify, its existence is impossible to ignore. The violence seems to be concentrated in a number of municipal areas, but violence can occur in any community. Certainly, even mass casualties have become part of our everyday life.

In 2016, homicides and nonfatal shootings increased dramatically relative to 2015. In 2017, we are tracking a 40% increase in homicides and a 30% increase in nonfatal shootings—particularly concerning when one considers that these numbers are being compared to the previously increased 2016 statistics.

Many community EDs are not accustomed to dealing with a significant volume of penetrating trauma, and thus they may not be as familiar with the newest means of resuscitation, evaluation, and treatment of these injuries. It will be important for every medical center to do what is necessary to be able to effectively triage and provide initial treatment for patients with penetrating trauma.

The victims of penetrating trauma are often young, and unfortunately, despite our best efforts, these patients often die in the ED. This creates a huge emotional burden on people who work in the ED, particularly those who are not used to seeing large volumes of gunshot wounds (GSWs) or stab wounds. Even those of us working in busy urban trauma centers feel the emotional

burden of this new epidemic. Each of us will need to cope with these issues and help each other deal with them.

It is important to recognize the dramatic change in trauma demographics over the last few years, and make plans to care for the changing face of trauma to optimize results and save as many lives as possible. In part 1 of our 2-part, "The Changing Landscape of Trauma Care," we focus on the specific issues and concerns encountered in elderly trauma patients, as well as victims of all ages presenting with penetrating trauma from stab and GSWs.

Trauma in the Elderly Population

There has been and continues to be an increase in the elderly population in the United States. In 2014, 46 million Americans representing 15% of the total population were older than age 65 years.[1] Of all age groups in the United States, the elderly population is one of the fastest growing and, according to the 2010 Census, grew at a faster rate than in previous years.[2] This growth is expected to continue as many of the post-World War II baby boomer generation age. By the year 2030, an estimated 1 in 5 Americans will be older than 65 years of age—representing a 7% absolute increase from 2010 to 2030.[1]

Furthermore, men and women in this population are maintaining an active lifestyle well into their seventh and eighth decade, which has led to an increased incidence of trauma in this age group, primarily from falls and low-velocity MVCs. According to data from the National Trauma Data Bank in 2016, nearly 43% of all traumatic incidents occurred in patients older than age 55 years, as compared to only 32% in 2010.[3,4] Today, injury is the seventh leading cause of death among the elderly population.[5]

Pre-existing Conditions and Comorbidities

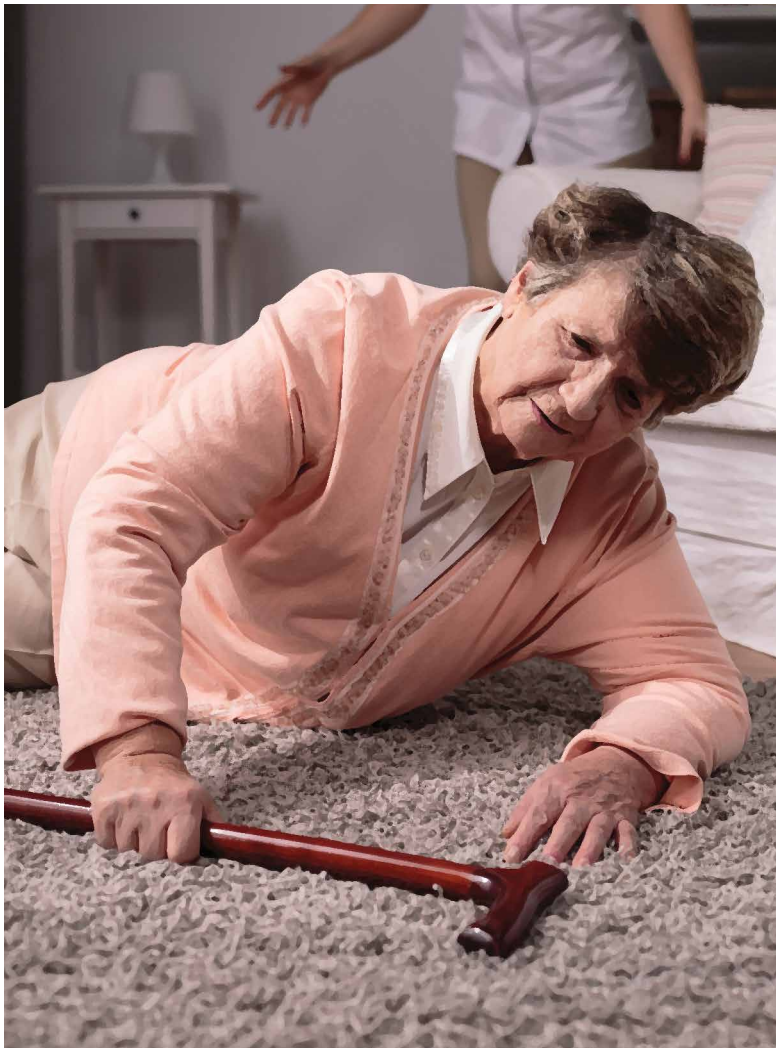
The elderly population tends to have more complex medical histories, with pre-existing conditions and comorbidities—both of which result in intolerance to alterations from normal physiology after acute trauma and may place them at risk for complications and death. This point was highlighted in an invited commentary by one of us (TS) over 20 years ago, in which he stated, "Resting organ function often is preserved, but the ability to augment performance in response to stress is greatly compromised."[6]

Studies in the early 1990s established a link between trauma outcomes and comorbidities.[7-9] Morris et al[7] found that ischemic heart disease, diabetes, chronic obstructive pulmonary disease, congenital coagulopathy, and cirrhosis highly influence trauma outcomes. They also noted that 25% of trauma patients over age 65 years had at least one of these five comorbidities and were nearly two times more likely to die. These findings were confirmed in 2002 by Grossman et al,[8] who demonstrated that each year over age 65 years held a mortality increase of 6.8%.[8] Additionally, they found that congestive heart failure, cancer, renal disease, and hepatic disease were the comorbidities with the highest impact on mortality.[8]

The presence of pre-existing conditions or comorbidities has also been associated with increased risk for complications, and subsequent increased mortality. In 2010, Aitken et al[9] found that 6.2% of elderly trauma patients developed pneumonia postinjury, which was associated with increased intensive care unit (ICU) and hospital length of stay. Pre-existing pulmonary disease and higher Injury Severity Scores (ISS) were also found to be risk factors, demonstrating a 5.9% incidence of acute kidney injury in this group, conferring a 10-fold increased risk of mortality.

In efforts to improve outcomes in elderly trauma patients, many centers have integrated geriatric consults in the ED for all patients over a certain age, following injury. Though Olufajo et al[10] were unable to demonstrate an in-house or 30-day mortality benefit after implementing a mandatory geriatrics consult for patients over age 70 years, they did show a nonstatistically significant trend toward fewer ICU readmissions with the consults.

In 2001, Demetriades et al[11] reported a 50% mortality rate among patients aged 70 years and older who met criteria for full trauma team activation. Interestingly, the mortality rate for patients over age 70 years was 24%, compared to 7.6% for younger patients admitted during the same period. Those in the 70 years and older age group who did not meet criteria for full trauma team activation still had a 16% mortality rate, and 24% required ICU admission.



© Photographee.eu/Shutterstock

Demetriades et al[11] also demonstrated that prehospital/admission vital signs in patients 70 years and older were often normal but misleading. In this group, 63% of patients with an ISS greater than 15, and 25% with an ISS greater than 30 did not have tachycardia or hypotension criteria for full trauma activation.[11] These findings have led to recommendations for a lower threshold for trauma activations in geriatric patients.[12]

Recent studies have suggested that adding an age threshold to the trauma activation criteria may improve outcomes without leading to an unacceptable overtriage rate. In 2016, Hammer, et al[13] reported improved outcomes, with only 2% of patients being overtriaged, when they added to their trauma activation criteria an age threshold of 70 years, regardless of physiology or mechanism of injury. They ultimately concluded that it was appropriate and cost-effective. In 2017, Cooper et al[14] published a position paper on the Geriatric Trauma Coalition (GeriTraC) covering the convergence of aging and injury. The mission of GeriTraC is to improve geriatric trauma care from prevention to transition of care.[14]

Fall-Related Trauma

Falls are the most common cause of fatal and nonfatal injury in patients over age 65 years.[15] Most fall injuries occur at home and during the winter months, and tend to be from ground level.[16] Although most result in only minor trauma, many cause significant injuries requiring hospitalization. In 2006, Stevens et al[17] estimated that both fatal and nonfatal falls in the elderly accounted for almost $20 billion in direct medical costs.

Motor Vehicle Collisions

Motor vehicle collisions/pedestrian struck are the second most significant causes of fatal and nonfatal injury in elderly patients. Older drivers who are hospitalized following an MVC have significantly longer hospital lengths of stay and an overall higher mortality rate.[16] Elderly patients are more likely to be victims of "pedestrian-struck-by-vehicle" due to their decreased visual and auditory acuity, reduced reaction time, slower movement, and confusion.

© Keith Muratori/Shutterstock

Suicide

Suicide is the third leading cause of injury-related death for those aged 65 years and older.[15] Risk factors for suicide in the elderly population include psychiatric disorders, particularly depression; medical conditions, especially cancer or chronic lung disease; moderate-to-large alcohol use; and social isolation. Changes in behavior, such as altering a will, new preoccupation with religion, or giving away life possessions, may be warning signs of impending suicide.

Novel Oral Anticoagulants

Many people, both old and young, are taking oral anticoagulants for various conditions. Warfarin has traditionally been the medication of choice, with readily available reversal agents, if needed. However, the development of NOACs, which antagonize activity of a single step in the coagulation cascade, has presented trauma care providers with a new challenge in achieving hemostasis. The NOACs include a direct thrombin inhibitor (dabigatran), and the Factor Xa (FXa) inhibitors (apixaban, edoxaban, and rivaroxaban). These NOACs have been shown to be as effective as traditional vitamin K antagonists (warfarin) with a comparable or lower spontaneous risk of bleeding. Along with an acceptable safety profile, these drugs cause significantly less drug and food interactions and are easier to dose, with no need for monitoring levels.[18] Since the arrival of the first NOAC dabigatran in 2010, use of these drugs has continued to increase, and are becoming more popular in the treatment of venous thromboembolism in younger patients as well. A study by Desai et al[19] examining newly initiated anticoagulation for AF between 2010 and 2013 found that 62% of all new anticoagulant prescriptions were for NOACs.

Hemostasis Challenges

Because of the lack of reversal agents or antidotes available, the NOACs present a unique challenge and major concern when anticoagulation properties must be reversed quickly. Among the NOACs, dabigatran is the only NOAC that is 35% protein bound and can be effectively cleared by hemodialysis (HD). Rivaroxaban and apixaban, in contrast, are highly protein bound (95% and 87%, respectively), which renders HD ineffective for clearance. Even for dabigatran, though HD may be a treatment option in the presence of potentially life-threatening bleeding associated with dabigatran alone, this is only a possibility if the patient's hemodynamics can tolerate HD.

Extrapolating from experience with war-

To date, there are no commercially available antidotes or reversal agents for the FXa inhibitors, though two promising agents are in various phases of clinical trials.

farin-associated bleeding, the use of FFP, PCC, and recombinant activated factor VII for NOAC-associated bleeding has been proposed and attempted.[20] Though FFP may be necessary to restore circulating blood volume as part of a massive transfusion protocol in a patient with NOAC-associated hemorrhage, it is generally not a reasonable sole strategy for reversal of NOACs because the coagulation factors in FFP are not present in high enough concentrations to be effective.[18]

Prothrombin Complex Concentrates

Three- and Four-Factor PCCs. Four-factor PCC (4F-PCC), which became available for use in the United States in April 2013, contains concentrated amounts of all four of the vitamin K dependent factors (II, VII, IX, and X), as well as proteins C and S. Three-factor PCC (3F-PCC) does not contain significant levels of factor VII,[20] and preclinical studies on its efficacy in reversing NOACs have not been consistent.

Early studies using animal models showed promising results for both 3F-PCC and 4F-PCC in correcting derangements in laboratory coagulation markers as well as observed bleeding time.[21-23] However, other animal studies failed to demonstrate an improvement in observed bleeding time or volume despite full or partial correction of coagulation studies after PCC.[24,25] In human studies, PCC has been observed to correct some laboratory parameters of coagulation, but not others.[26,27] Thus far, these studies have been limited to healthy volunteers without active bleeding and have been largely ex vivo and in vitro studies, so it is difficult to determine if the demonstrated correction of coagulation studies translates into clinical benefit. Both 3F-PCC and 4F-PCC have shown promise, though studies with 4F-PCC have yielded more consistent results.[26,27]

Activated PCC. Activated PCC (aPCC), which contains the same vitamin K dependent factors (factors II, VII, IX, X) with some in their activated form, has shown similar results. In fact, ex vivo and in vitro studies thus far seem to suggest that aPCC is more effective than PCC in correcting coagulation test parameters, as well as thrombin generation indices.[28-31] However, an aPCC has also been demonstrated to be more procoagulant and, thus, may increase the risk of thrombotic complications.[32]

Recombinant Activated Factor VII

Recombinant activated factor VII has shown less promise than PCC or aPCC in the reversal of NOAC-associated bleeding. Additionally, similar to aPCC, it may increase the risk of thrombosis.[20,33]

Monoclonal Antibody Agent

In October 2015, the US Food and Drug Administration approved idarucizumab, a monoclonal antibody agent for the reversal of dabigatran. Idarucizumab has a binding affinity approximately 350 times higher than the binding affinity of dabigatran for thrombin with no demonstrated procoagulant effects.[20] To date, there are no commercially available antidotes or reversal agents for the FXa inhibitors, though two promising agents are in various phases of clinical trials. The first, andexanet alfa, is a modified, recombinant factor X which binds FXa inhibitors with high affinity. This agent has shown promising results in the reversal of apixaban and rivaroxaban.[20] The second is called aripazine (PER977) and has the potential to reverse unfractionated heparin, low molecular weight heparins, fondaparinux, FXa inhibitors, and thrombin inhibitors. Early in vivo human studies have been promising.[18]

Currently, there are no well-designed clinical studies examining the use of PCC for NOAC reversal in trauma. There are only a few published case reports, showing both successful and unsuccessful results, and a small retrospective series of only 18 patients specifically looking at both traumatic and spontaneous intracranial hemorrhage.[34-37] There are also no universally agreed upon published guidelines

for the management of NOAC-associated bleeding in the absence of drug-specific reversal agents.

Penetrating Trauma

The United States leads all high-income nations in GSW mortality,[38] and its rate of firearm homicide is almost 20 times that of other high-income countries. In 2014, there were more than 33,000 firearm-related deaths in the United States, almost two-thirds of which were suicide-related.[38] These numbers represent 16.8% of all deaths from injury. For each fatal firearm injury, there were nearly two nonfatal firearm injuries (65,106) the same year.[39] Since 2001, the leading cause of death among black males aged 15 to 44 years has been firearm-related homicide. In 2015, that age demographic was lowered to include 10- to 14-year-old black males. In 2015, suicide by firearm was the second leading cause of death among white males over the age of 55 years and the third leading cause of death among white males aged 10 to 54 years.[40]

Incidents of gun violence are on the rise. These incidents are becoming more frequent and more often fatal. In a retrospective review of their trauma registry, as well as county records, Sauaia et al[41] examined trends of GSW severity and mortality in Denver, Colorado from 2000 to 2013. They noted the proportion of GSW admissions remained stable over time, but injury severity and mortality from GSWs increased significantly, contrary to mortality and survival trends for all other injury mechanisms.[41]

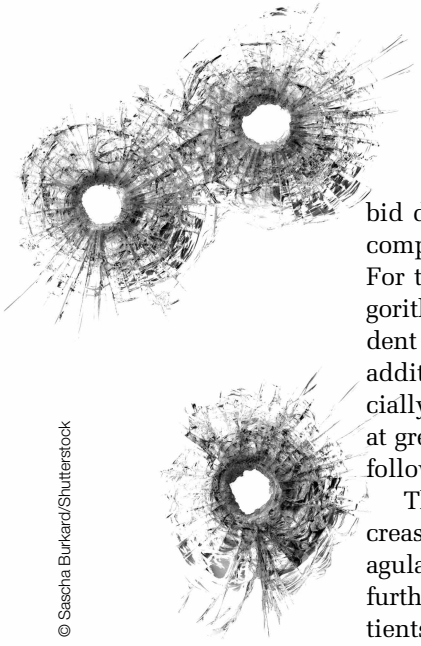
The increasing GSW severity and mortality trend is not unique to Denver. Many media sources in cities across the country have reported similar statistics obtained from their local police departments in the past year. Though gun violence is a subject that is in desperate need of prevention research, current legislation makes these studies challenging to undertake. In 1996, Congress passed the Dickey Amendment to the Omnibus Consolidated Appropriations Act for the 1997 fiscal year, which

© mark reinstein/Shutterstock

states that "none of the funds made available for injury prevention and control at the Centers for Disease Control and Prevention may be used to advocate or promote gun control."[42,43] In the 2011 Consolidated Appropriations Act for the fiscal year 2012, this restriction was expanded to include the National Institutes of Health (NIH).[44,45] These measures largely explain the paucity of primary research in gun violence in the last two decades—despite the increasing role and costs gun violence contributes to the US health care system. Gun violence is an epidemic, and like all other epidemics in the United States, it requires government-funded research to help protect the people.[44]

Conclusion

The last decade has seen some significant changes in trauma demographics in the United States. As the population of US men and women older than age 65 years continues to grow, trauma can no longer be considered a disease of young people. In addition to elderly men and women being more active than ever before, comor-



bid diseases place them at higher risk for complications and death following injury. For these reasons, many trauma triage algorithms now include age as an independent factor in activating a trauma alert. In addition to age, medications, and especially polypharmacy, can place patients at greater risk of injury and complications following trauma.

The last 10 years also has seen an increase in the number of patients on anticoagulants. The development of the NOACs further complicates the care of trauma patients taking these medications. Although designed to simplify care for patients and providers by minimizing bleeding risks and eliminating blood monitoring, there are only limited, and sometimes no reliable reversal agents available for NOACs, creating challenges when treating trauma patients who are on these medications. Finally, despite efforts by many individuals and groups, gun violence still remains a large and growing problem in the United States. Hopefully, continued efforts of national, state and local programs will begin to improve the current situation.

Editor's Note: *Part 2 of* "The Changing Landscape of Trauma Care" *will appear in the August 2017 issue of* Emergency Medicine *and will cover the changes in strategies and techniques to care for injured patients.*

References

1. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2016: key indicators of well-being. US Gov Print Off; Washington, DC. 2016; August. https://agingstats.gov/docs/LatestReport/Older-Americans-2016-Key-Indicators-of-WellBeing.pdf. Accessed June 8, 2017.
2. Howden L, Meyer J. Age and sex composition: 2010. 2010 Census Briefs. 2011;(May):1-16. http://www.census.gov/library/publications/2011/dec/c2010br-03.html. Accessed June 8, 2017.
3. American College of Surgeons Committee on Trauma. National Trauma Data Bank 2010 Annual Report. 2010:1-93. https://www.facs.org/~/media/files/quality%20programs/trauma/ntdb/ntdbannualreport2010.ashx. Accesssed June 8, 2017.
4. American College of Surgeons Committee on Trauma. National Trauma Data Bank 2016 Annual Report. 2016:1-147. https://www.facs.org/~/media/files/quality%20programs/trauma/ntdb/ntdb%20annual%20report%202016.ashx. Accessed June 8, 2017.
5. Health, United States 2015. With Special Feature on Racial and Ethnic Health Disparities. US Department of Health and Human Services. Centers for Disease Control and Prevention. 2016:126. https://www.cdc.gov/nchs/data/hus/hus15.pdf. Accessed June 8, 2017.
6. Scalea TM. Invited commentary (for McMahon DJ, William S, Kauder D. Comorbidity and trauma in the elderly. *World J Surg.* 1996;20(8):116. doi:10.1007/s002689900170.
7. Morris JA Jr, MacKenzie EJ, Edelstein SL. The effect of preexisting conditions on mortality in trauma patients. *JAMA.* 1990;263(14):1942-1946.
8. Grossman MD, Miller D, Scaff DW, Arcona S. When is an elder old? Effect of preexisting conditions on mortality in geriatric trauma. *J Trauma.* 2002;52(2):242-246.
9. Aitken LM, Burmeister E, Lang J, Chaboyer W, Richmond TS. Characteristics and outcomes of injured older adults after hospital admission. *J Am Geriatr Soc.* 2010;58(3):442-449. doi:10.1111/j.1532-5415.2010.02728.x.
10. Olufajo OA, Tulebaev S, Javedan H, et al. Integrating geriatric consults into routine care of older trauma patients: one-year experience of a level I trauma center. *J Am Coll Surg.* 2016;222(6):1029-1035. doi:10.1016/j.jamcollsurg.2015.12.058.
11. Demetriades D, Sava J, Alo K, et al. Old age as a criterion for trauma team activation. *J Trauma.* 2001;51(4):754-756; discussion 756-757.
12. Calland JF, Ingraham AM, Martin N, et al; Eastern Association for the Surgery of Trauma. Evaluation and management of geriatric trauma: an Eastern Association for the Surgery of Trauma practice management guideline. *J Trauma Acute Care Surg.* 2012;73(5 Suppl 4):S345-S350. doi:10.1097/TA.0b013e318270191f.
13. Hammer PM, Storey AC, Bell T, et al. Improving geriatric trauma outcomes: A small step toward a big problem. *J Trauma Acute Care Surg.* 2016;81(1):162-167. doi:10.1097/TA.0000000000001063.
14. Cooper Z, Maxwell CA, Fakhry SM, et al. A position paper: The convergence of aging and injury and the need for a Geriatric Trauma Coalition (GeriTraC). *J Trauma Acute Care Surg.* 2017;82(2):419-422. doi:10.1097/TA.0000000000001317.
15. Centers for Disease Control and Prevention. Web-based injury statistics query and reporting system (WISQARS). National Center for Injury Prevention and Control, Centers for Disease Control and Prevention. http://www.cdc.gov/injury/wisqars/index.html. Updated June 1, 2017. Accessed June 8, 2017.
16. Menaker J, Scalea TM. Care of the injured elderly. In Rosenthal RA, Zenilman K, Katlic MR, eds. *Principles and Practice of Geriatric Surgery.* 2nd ed. Springer: New York, NY: Springer; 2011:391-410.
17. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev.* 2006;12(5):290-295. doi:10.1136/ip.2005.011015.
18. von Heymann C, Rosenthal C, Kaufner L, Sander M. Management of direct oral anticoagulants-associated bleeding in the trauma patient. *Curr Opin Anaesthesiol.* 2016;29(2):220-228. doi:10.1097/ACO.0000000000000294.
19. Desai NR, Krumme AA, Schneeweiss S, et al. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation- quality and cost implications. *Am J Med.* 2014;127(11):1075-1082.e1. doi:10.1016/j.amjmed.2014.05.013.

20. Marano G, Vaglio S, Pupella S, Liumbruno GM, Franchini M. How we treat bleeding associated with direct oral anticoagulants. *Blood Transfus.* 2016;14(5):465-473. doi:10.2450/2016.0180-15.
21. Zhou W, Schwarting S, Illanes S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke.* 2011;42(12):3594-3599. doi:10.1161/STROKEAHA.111.624650.
22. Pragst I, Zeitler SH, Doerr B, et al. Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. *J Thromb Haemost.* 2012;10(9):1841-1848. doi:10.1111/j.1538-7836.2012.04859.x.
23. van Ryn J, Schurer J, Kink-Eiband M, Clemens A. The successful reversal of dabigatran-induced bleeding by coagulation factor concentrates in a rat tail bleeding model do not correlate with ex vivo markers of anticoagulation. *Blood.* 2011;118(2316).
24. Herzog E, Kaspereit F, Krege W, Joanne R Van, Dickneite G, Pragst I. Non-clinical safety and efficacy of prothrombin complex concentrates (pcc) for the reversal of dabigatran mediated anticoagulation. *J Thromb Haemost.* 2013;11:693.
25. Godier A, Miclot A, Le Bonniec B, et al. Evaluation of prothrombin complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. *Anesthesiology.* 2012;116(1):94-102. doi:10.1097/ALN.0b013e318238c036.
26. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation.* 2011;124(14):1573-1579. doi:10.1161/CIRCULATIONAHA.111.029017.
27. Escolar G, Fernandez-Gallego V, Arellano-Rodrigo E, et al. Reversal of apixaban induced alterations in hemostasis by different coagulation factor concentrates: significance of studies in vitro with circulating human blood. *PLoS One.* 2013;8(11):e78696. doi:10.1371/journal.pone.0078696.
28. Galan AM, Arellano-Rodrigo E, Sanz V, et al. Effects of rivaroxaban and dabigatran on hemostasis and reversion of their antithrombotic effects by different coagulation factors: evidence raised from a clinical study in healthy volunteers. *J Thromb Haemost.* 2013;11:418-419.
29. Escolar G, Arellano-Rodrigo E, Lopez-Vilchez I, et al. Reversal of rivaroxaban-induced alterations on hemostasis by different coagulation factor concentrates—in vitro studies with steady and circulating human blood. *Circ J.* 2015;79(2):331-338. doi:0.1253/circj.CJ-14-0909.
30. Perzborn E, Gruber A, Tinel H, et al. Reversal of rivaroxaban anticoagulation by haemostatic agents in rats and primates. *Thromb Haemost.* 2013;110(1):162-172. doi:10.1160/TH12-12-0907.
31. Chan HHW, Atkinson HM, Goncharenko M, Berry LR, Chan AKC. Reversal of dabigatran using recombinant activated factor VII and activated prothrombin complex concentrates in thromboelastography assay. *J Thromb Haemost.* 2011;9:576-577.
32. Hoffman M, Monroe DM. Reversing targeted oral anticoagulants. *Hematology Am Soc Hematol Educ Program.* 2014;2014(1):518-523. doi:10.1182/asheducation-2014.1.518.
33. Marlu R, Hodaj E, Paris A, Albaladejo P, Cracowski JL, Pernod G. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. *Thromb Haemost.* 2012;108(2):217-224. doi:10.1160/TH12-03-0179.
34. Grandhi R, Newman WC, Zhang X, et al. Administration of 4-factor prothrombin complex concentrate as an antidote for intracranial bleeding in patients taking direct factor xa inhibitors. *World Neurosurg.* 2015;84(6):1956-61. doi:10.1016/j.wneu.2015.08.042.
35. Durie R, Kohute M, Fernandez C, Knight M. Prothrombin complex concentrate for the management of severe traumatic bleeding in a patient anticoagulated with apixaban. *J Clin Pharm Ther.* 2016;41(1):92-93. doi:10.1111/jcpt.12339.
36. Kauffmann S, Chabanne R, Coste A, et al. Favorable outcome of rivaroxaban-associated intracerebral hemorrhage reversed by 4-factor prothrombin complex concentrate: impact on thrombin generation. *A&A Case Rep.* 2015;4(11):151-154. doi:10.1213/XAA.0000000000000143.
37. Maurice-Szamburski A, Graillon T, Bruder N. Favorable outcome after a subdural hematoma treated with feiba in a 77-year-old patient treated by rivaroxaban. *J Neurosurg Anesthesiol.* 2014;26(2):183. doi:10.1097/ANA.0000000000000030.
38. Richardson EG, Hemenway D. Homicide, suicide, and unintentional firearm fatality: comparing the United States with other high-income countries, 2003. *J Trauma.* 2011;70(1):238-243. doi:10.1097/TA.0b013e3181dbaddf.
39. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Deaths: final data for 2014. *Natl Vital Stat Rep.* 2016;65(4):1-122. https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf. Accessed June 8, 2017.
40. Centers for Disease Control and Prevention. Leading causes of death reports, national and regional, 1999-2015. https://webappa.cdc.gov/sasweb/ncipc/leadcaus10_us.html. Accessed June 8, 2017.
41. Sauaia A, Gonzalez E, Moore HB, Bol K, Moore EE. Fatality and severity of firearm injuries in a denver trauma center, 2000-2013. *JAMA.* 2016;315(22):2465-2467. doi:10.1001/jama.2016.5978.
42. Omnibus Consolidated Appropriations Bill. HR 3610, Pub L No. 104-208. http://www.gpo.gov/fdsys/pkg/PLAW-104publ208/pdf/PLAW-104publ208.pdf. September 1996. Accessed June 13, 2017.
43. Kellermann AL, Rivara FP. Silencing the science on gun research. *JAMA.* 2013;309(6):549-550. doi:10.1001/jama.2012.208207.
44. Consolidated Appropriations Act of 2012. HR 2055: Pub L No. 112-174. https://www.gpo.gov/fdsys/pkg/PLAW-112publ74/pdf/PLAW-112publ74.pdf. December 2011. Accessed June 13, 2017.
45. Rubin R. Tale of 2 agencies: CDC avoids gun violence research but NIH funds it. *JAMA.* 2016;315(16):1689-1691. doi:10.1001/jama.2016.1707.
46. Cook A, Osler T, Hosmer D, et al. Gunshot wounds resulting in hospitalization in the United States: 2004-2013. *Injury.* 2017;48(3):621-627. doi:10.1016/j.injury.2017.01.044.