WestJEM

Volume 20, Number 5, September 2019 Open Access at *West*JEM.com ISSN 1936-900X

Western Journal of Emergency Medicine:

Integrating Emergency Care with Population Health

Indexed in MEDLINE

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VOLUME 20, NUMBER 5, September 2019

PAGES 690-841


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Editorial and Publishing Office: *West*JEM/Depatment of Emergency Medicine, UC Irvine Health, 333 City Blvd, West, Rt 128-01, Orange, CA 92868, USA
Office: 1-714-456-6389; Email: Editor@westjem.org

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Editorial and Publishing Office: *West*JEM/Depatment of Emergency Medicine, UC Irvine Health, 333 City Blvd, West, Rt 128-01, Orange, CA 92866, USA

Office: 1-714-456-6389; Email: Editor@westjem.org

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JOURNAL FOCUS

Emergency medicine is a specialty which closely reflects societal challenges and consequences of public policy decisions. The emergency department specifically deals with social injustice, health and economic disparities, violence, substance abuse, and disaster preparedness and response. This journal focuses on how emergency care affects the health of the community and population, and conversely, how these societal challenges affect the composition of the patient population who seek care in the emergency department. The development of better systems to provide emergency care, including technology solutions, is critical to enhancing population health.

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Boarding of Mentally Ill Patients in Emergency Departments: American Psychiatric Association Resource Document

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Section Editor: Marc L. Martel, MD
Submission history: Submitted January 19, 2019; Revision received June 3, 2019; Accepted June 3, 2019
Electronically published July 22, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.6.42422

The treatment of severe mental illness has undergone a paradigm shift over the last 50 years, away from a primary emphasis on hospital-based care and toward community-based care. Some of the forces driving this deinstitutionalization have been scientific and patient-centered, such as better differentiation between acute and subacute risk, innovations in outpatient and crisis care (assertive community treatment programs, dialectical behavioral therapy, treatment-oriented psychiatric emergency services), gradually improving psychopharmacology, and an increased appreciation of the negative effect of coercive hospitalization, except when risk is very high. On the other hand, some of the forces have been less focused on patient needs: budget-driven cuts in public hospital beds divorced from population-based need; managed care's profit-driven impact on private psychiatric hospitals and outpatient services; and purported patient-centered approaches promoting non-hospital care that may under-recognize that some extremely ill patients need years of painstaking effort to make a community transition.

The result has been a reconfiguration of the country's mental health system that, at times, leaves large numbers of people without adequate mental health and substance abuse services. Often their only option is to seek care in medical emergency departments (ED) that have not been designed for the needs of mentally ill patients. Increasingly, many of those individuals end up waiting in EDs for appropriate care and disposition for hours or days. This overflow phenomenon has become so prevalent that it has been given a name: "boarding." This practice is almost certainly detrimental to patients and staff, and it has spawned efforts on multiple fronts to understand and resolve it. When considering solutions, both ED-focused and systemwide considerations must be explored. This resource document provides an overview and recommendations regarding this complex topic. [West J Emerg Med. 2019;20(5)690-695.]

INTRODUCTION

The Scope of the Problem

With "deinstitutionalization" of psychiatric patients in the 1960s, and the advent of managed care starting in the 1980s, the emphasis of caring for persons with mental disorders has shifted away from state-run facilities and toward both in- and out-patient, community-based treatment facilities. This has led to market forces, rather than population indices, driving down the total number of inpatient psychiatric beds. The trend toward fewer beds, which decreases further during periods of economic downturn, has resulted in more psychiatric care taking place in emergency departments (ED) that may be ill-equipped to handle mentally ill patients. When considering solutions, both ED and systemwide considerations must be explored to reduce inappropriate "boarding" of psychiatric patients in the ED and to improve care.

At the core of the problem is the fact that in recent years more and more patients find themselves seeking care for psychiatric illness in EDs. The annual number of all-cause ED visits has continued to increase[1,2] with 6-10% of patients presenting for psychiatric illness and related concerns.[3,4] This is considered a "small but increasing subset" of the ED visit population.[4] Psychiatric visits weigh heavily on the ED system. They have been found to occupy more time (42% longer than non-psychiatric visits), result in increased inpatient admission (24% vs 12%) and transfer (16% vs 1%), and occupy a higher percentage of self-pay or charity care (22% vs 16%) compared to non-psychiatric visits.[5] Furthermore, the duration of time spent in the ED is especially long for patients who require transfer to a different facility or who carry a diagnosis of significant mental illness or substance use disorder.[5]

The term "ED boarding" is subject to interpretation, as there is not one agreed-upon definition. Some have described boarding as the situation that occurs when patients remain in the ED for four or more hours after the decision has been made to admit.[6] Others define it as a stay in the ED exceeding 24 hours.[7] Nolan and colleagues went further in their definition to an actual description stating: "Boarding describes ED patients whose evaluation is complete and for whom the decision has been made to either admit or transfer, but for whom there is no available bed."[8] This is quite similar to the language used by The Joint Commission, which has defined boarding as, "patients being held in the emergency department or another location after the decision to admit or transfer has been made."[9] Although the term is used for all patients awaiting hospitalization, the situation is more ominous for patients with psychiatric issues. One survey revealed that 11% of all ED patients were boarded but 21.5% of all psychiatric ED patients were boarded, and odds of boarding for psychiatric patients were 4.78 (2.63-8.66) times higher than non-psychiatric patients.[8]

A 2008 survey of 1400 ED directors by the American College of Emergency Physicians (ACEP) found 79% of the 328 respondents reported having psychiatric patients boarding in their EDs; 55% of ED directors reported boarders on a daily or at least multiple days per week basis; and 62% reported that there are no psychiatric services involved with the patient's care while they are being boarded prior to their admission or transfer.[6] Published average boarding times have ranged from 6.8 hours to 34 hours.[10-11] Fundamentally, then, for psychiatric patients "boarding" means spending extensive time in inappropriate locations – whether in the ED on an inpatient medical floor, or in another equally unsuitable place – while awaiting voluntary or involuntary psychiatric hospitalization.[8]

Multiple factors contribute to the ED boarding of psychiatric patients, ranging from large societal challenges and hospital-systems issues to individual patient characteristics. Although the most frequently cited cause of ED boarding is inpatient bed shortages, the problem really starts much farther upstream. Insufficient funding for lower levels of care from basic community clinics to intensive outpatient programs, community crisis stabilization units, and respite services fuels the crisis and leads patients to seek care in emergency settings. Of the respondents to the ACEP survey, 23% replied they have no accessible community psychiatric resources and 59% had no substance abuse or dual-diagnosis patient services available.[6] Absence of alternative placement options aside from admission is only one of many constraints facing patients.[12]

Other social factors contributing to delays for patients seeking care in the ED may include the lack of insurance or public insurance, hesitation of private hospitals in accepting un/underinsured patients, lack of ambulances willing to provide transport, time spent handling preauthorization from insurance carriers and other managed care hurdles, homelessness, and difficulty in placing patients with severe psychiatric illness burden.[13-14] Added to this public health systems deficit is the inadequate number of state psychiatric inpatient beds due to funding cuts, inpatient unit closures and bed reductions. Delays in discharge for patients already admitted to psychiatric units awaiting limited outpatient services contribute further to the problem.[15] And, like the larger world of which it is a microcosm, the ED itself often provides a dearth of available mental health resources. There may be no therapeutic milieu, programming, or consistent provider teams such as are available on inpatient psychiatric units.[16] Indeed, there are often too few or no psychiatric providers at all in emergency settings.[13] Many times ED personnel are on their own to determine acute treatment plans for significantly ill psychiatric patients. Some emergency providers may harbor concerns about their liability in treating psychiatric patients.[17]

This lack of treatment provided to patients psychiatrically boarding is a major concern. As noted previously, 62% of ED medical directors responding to the ACEP survey reported that there are no psychiatric services involved with the patient's care while he or she is being boarded prior to admission or transfer.[6] Boarded patients tend to have higher rates of psychotic and personality disorders, and are more likely to require physical restraints/seclusions.[16] Due to its loud and chaotic nature, the ED environment can exacerbate underlying conditions.[15] Iatrogenic worsening of symptoms due to suboptimal ED conditions is not uncommon.[15] Timely, active interventions can reduce patient anxiety, frustration, and agitation, and may even obviate the need for some admissions.[15]

ED boarding carries a high cost burden, affecting the system and patients in a variety of ways. The average monetary cost to an ED to board a psychiatric patient has been estimated at $2,264.[4] Beyond the direct monetary costs, the system becomes less efficient. In general, ED boarding contributes to reduced ED capacity, decreased availability of emergency staff, longer wait times for all patients in waiting rooms, increased patient frustration, and increased pressure on staff. Psychiatric patients may require increased use of ancillary support (such as security officers or safety attendants), especially if they are agitated and because they have a statistically increased elopement risk.[4] On the whole for the ED system, boarding results in increased rates of

patients who leave without being seen, longer inpatient stays for those admitted, as well as lost hospital revenue and consumption of ED resources.[4,8,12,15] Providers experience a higher degree of stress related to boarding of patients, resulting in a greater risk of adverse events, and lower levels of reported patient satisfaction.[10] Emergency physicians and nurses may carry negative attitudes toward psychiatric patients that in turn can affect the treatment they provide and may lead to adverse outcomes.[18]

Many different solutions to the crisis of ED boarding of patients have been proposed. These include increasing resources such as crisis stabilization units, inpatient beds and mental health resources within medical EDs, as well as increasing funding to outpatient mental health services. In addition, expanding the reach of existing psychiatric resources through telepsychiatry and the diversion of patients to regional, specialized psychiatric emergency services that can allow for directed psychiatric care may have great benefit.[19,20] Ultimately, both ED and greater community and systemwide considerations must be explored to reduce ED boarding and improve patient care.

Potential Solutions: The Role of the Emergency Department

In reality, boarded patients in an ED may not only be awaiting an actualized disposition, but may also be awaiting care. To improve treatment and outcomes of psychiatric patients during the interval before inpatient hospitalization, EDs should consider several unique aspects of this population.

Rapid Treatment of Agitation

The etiology of agitation is broad and includes systemic medical, as well as psychiatric, causes. It is unwise to rely on a "single approach" for management. In the six-article *Western Journal of Emergency Medicine* series on Best Practices in the Evaluation and Treatment of Agitation, the American Association for Emergency Psychiatry (AAEP) supported non-coercive de-escalation as the primary intervention, with the goal being to calm, not sedate, the patient.[21] The calm patient may be better able to participate in care, while the sedated patient may awaken agitated, creating an ongoing cycle. Over-sedation is associated with prolonged ED visits[18] and potentially compromises care. Verbal de-escalation, as well as targeted medications should be considered in this treatment.[22,23]

Some recommend the use of an agitation rating scale as a tool to identify mild agitation and to prompt appropriate treatment.[18] Several rating scales are available with determination of the right scale for a hospital largely made by ease of use. It is essential to identify underlying medical etiologies precipitating agitation and to treat them appropriately.[24] Staff including emergency physicians, nurses and hospital security should be provided with regular training on the management of agitation including verbal de-escalation techniques. Similar to "Code Blue" teams, some hospitals have used specially trained teams to aid in de-escalation of highly agitated patients. Even though these teams may exist, training the entire clinical team on proper de-escalation is essential.

Minimization of Restraint and Seclusion Use

Physical restraints should be used only as a last resort,[25] with use limited to the least amount of time necessary. Restraints and seclusion can be quite traumatic for patients, and these interventions raise the risk for medical complications.[26] They also can negatively affect a patient's well-being and trust in care.

Evaluation of Medical Comorbidities

Rapid identification of medical needs is critical when any patient presents to an ED. For patients with mental illness, this is no exception. Unless there is a long, established history of a psychiatric illness for which the patient presents similarly with each episode, patients with psychiatric symptoms should first be considered to have one or more medical conditions that are contributing to the clinical presentation. Rapid identification is especially important for those patients who present with agitation.[24] Similarly, because of the importance of not overlooking "medical mimickers" of psychiatric illness, the AAEP's recently published consensus guidelines urge the psychiatric and ED communities to move away from the generic concept of "medical clearance." Evaluations specific to the patient's signs and symptoms should be undertaken, with results clearly communicated between the ED and any receiving facilities.[27]

Active Treatment of Psychiatric Illness

For patients who may require a prolonged stay in the ED, active treatment of the underlying illness should be initiated, rather than focusing care solely on mitigating agitation. Treatment can come in multiple forms, such as medication and brief therapies. If the patient is unable to relay information regarding past helpful treatments, obtaining collateral history from family or outside treatment providers can be useful. Short-term therapies may be both efficacious and practical, although they are often overlooked in the busy emergency setting. Even patients who originally present with suicidal ideation may be stabilized by solution-focused, supportive or family therapies, facilitating discharge home or to a lower level of care. EDs may wish to invest in having social workers or other staff receive training in these basic therapies.

Implementation of Observation Units

Observation units in the ED, in concert with active treatment, may help patients avoid the need for psychiatric hospitalization. Patients may present as agitated or suicidal if intoxicated or following an extreme psychosocial event such as a break up, the death of a loved one, or the loss of a job. Use of an observation unit, a safe place in which patients can achieve a sober state or work through strong emotions, may also enable discharge to a lower level of care.

Active Treatment for Substance Intoxication or Withdrawal

Similar to the need for active treatment of psychosis or suicidality, much can be done to treat substance intoxication or

withdrawal in the emergency setting. Intoxicated patients may present as agitated, confused, or out of control. Targeted and timely treatment for agitation and withdrawal is critical, and may be life-saving. Benzodiazepines are the treatment of choice for stimulant intoxication or alcohol withdrawal.[23]

Importantly, the intoxicated patient may also present with suicidality. Some emergency providers may believe that suicidal thoughts occur only in the context of the intoxication. However, patients should be re-evaluated for suicidal ideation once they have cleared from their intoxicated or withdrawal states. Many EDs have protocols for alcohol withdrawal management but less so for other substance withdrawal syndromes. Protocols ensuring proper monitoring and proactive treatment may improve symptoms, decrease total medication requirements, and limit total ED/hospital time. In addition, regardless of a patient's presentation from substance use, the ED evaluation provides an opportunity to intervene. Motivational interviewing, a well-established effective intervention technique, is simple, takes little time, and may lead to a patient's interest or willingness for more intensive treatment.

Improved Coordination and Communication Around Disposition

As discussed, patients who present in highly agitated or suicidal states may require inpatient psychiatric care; however, there are also times when they may not, if appropriate front-line treatment is provided. When admission to an inpatient facility is required, direct communication between ED and inpatient providers is the optimal way to ensure a successful transfer of care. It is ideal to have a predetermined guide for medical evaluation so that medical stability is achieved prior to transfer. Laboratory testing may be necessary, but should be specifically individualized to the patient and the presentation. Medication may be necessary to allow for calm patient transfer. If it is determined that a patient can safely be discharged to a lower level of care, it is most effective if this is fully arranged in the ED prior to discharge. Optimally, the ED team should provide a thorough hand-off to the outside provider.

Other Hospital-Centered Approaches

It is generally agreed that improved access to psychiatric services will result in better patient care and decrease the time to discharge. Unfortunately, six in ten ED directors report that psychiatric services are not available during the boarding period.[6,28] This may be improved by expanding access to psychiatric services through telepsychiatry and integration of care. Telepsychiatry is being more widely used in emergency settings, and many contracts allow for 24-hour availability of psychiatrists as consultants to the ED service. Similarly, healthcare integration is being increasingly introduced into the ED setting. There are several new models that occur locally, allowing for an embedded mental health team including staff psychiatrists to provide consultation either to care teams or directly to patients.

Where possible, improvements in the environment of the emergency setting may have great benefit for patients with psychiatric illness. Boarding in the chaotic, crowded, noisy, and confined spaces of an ED can be anxiety-provoking, distressing, and may potentially exacerbate psychiatric symptoms. The presence of security, continuous observation, and even being forced to wear hospital clothing can lead patients to feel a loss of control that results in an escalation of symptoms.[15] Mental health emergency room extension areas provide a therapeutic environment more conducive to caring for patients with psychiatric illness. For hospitals with higher volumes, designated psychiatric EDs specialized in emergency psychiatric care may allow for diversion from typical, medical-emergency facilities.[20]

Within hospitals, improvement in the management of patient flow may help to stave off some of the pressures leading to ED boarding. Bed managers or computerized bed management systems may help increase efficiency by managing inpatient capacity. Case managers in the ED can help aid in community disposition. It is incumbent upon hospital leadership to engage in exploring these options to overcome barriers and improve patient care. Finally, data collection and monitoring is essential if progress toward reducing ED boarding and improvement in the provision of care to boarded patients is to be made. This data can be shared with community partners to help determine further strategies for improvement.

Potential Solutions: Community Efforts

Confronting the ED boarding challenge will require community involvement at the local, state, and ultimately national level.

Determine Local Needs

The creation of a taskforce for key stakeholders to convene and coordinate needs for a local area may be an important first step. Stakeholders include dedicated leadership committed to caring for individuals with psychiatric and substance use illnesses. Psychiatric hospitals/units, EDs, crisis centers, mobile crisis services, outpatient mental health clinics, law enforcement, emergency medical services (EMS) groups, group homes, crisis stabilization units, consumer advocates, peer specialists, judges, and local government all constitute stakeholders.

One strategy to determine local needs is to systematically examine each circumstance resulting in ED boarding; this will help to identify precipitants and potential barriers. Causes for ED boarding generally fall into three categories: front-end, ED, and back-end. ED causes have been previously discussed. Front-end causes relate to the spectrum of community-based crisis care. Back-end issues relate more to disposition options and the presence of adequate community resources, including those for severely mentally ill with treatment-resistant or highly complex conditions. Front-end and back-end causes are most closely related to the community. As many patients are un- or underinsured, financial considerations must be clearly understood when dealing with community resources and how funding might be applied. By trending the causes of ED boarding from the front

to the back ends, resources can be allocated where they appear most needed, with data collected to evaluate whether the number of boarding patients decreases with such intervention.

Focus On Diversion and Coordination

Diversion of patients to preferred resources allows patients to enter the best system for their care. One way of facilitating diversion is by creating an EMS triage system, agreed upon locally, that directs patients to psychiatric hospitals, EDs, and crisis stabilization units, based on criteria. A recent consensus guideline by the AAEP outlines several such protocols.[29]

In addition, providing support to mobile crisis services (ED or psychiatry backup) may help identify resource options for patients in need before they require an ED visit. Checklists can be created such that group homes and nursing facilities can determine whether to engage mobile crisis services or EMS. For diversion to be successful, however, a spectrum of non-emergency levels of care must be created in the community. These may be walk-in centers, respite programs, or crisis stabilization units. In addition, coordination between EDs, mobile crisis, and non-emergency community resources is essential. Clinics, regardless of size, should have true on-call ability to coordinate after-hours care instead of merely recommending that patients with pressing needs on evenings or weekends present to the ED for care. Adequate care coordination resources for patients within the ED are needed to ensure that all patients have viable, timely, follow-up appointments. Rapid access by community mental health providers is essential.

State Involvement

State leaders are responsible for allocating Medicaid funds and block grants, and thus are a vital partner in finding workable solutions to the ED boarding dilemma. Efforts need to focus on improved access to care through funding gaps identified in the analysis of boarding cases. This funding should increase the breadth of alternatives to EDs for crisis treatment such as mobile crisis units, crisis stabilization units, 24-hour walk-in clinics, and short-term residential facilities. Within the ED environment, funding can increase accessibility to telepsychiatry. Improved funding should coincide with measurement-based care including metrics and audits to ensure meaningful impact. Improved reimbursement for care with a focus on parity for mental illness, substance use disorders, and intellectual and developmental disorders will be critical.

In addition to providing financial resources, state governments can help to eliminate or safeguard against laws that decrease communication between healthcare providers, especially state laws that are more restrictive than the Health Insurance Portability and Accountability Act (HIPAA) and that effectively block communication between emergency physicians and community mental health centers. Reductions in other undue legal burdens, such as informed consent for emergency telepsychiatry, would also help in increasing access to care within EDs.

National Involvement

Government and professional organizations can also play an important role in solving problems related to ED boarding. Efforts should focus on increased access to lower levels of care. Groups should especially focus on developing funding models that support and stimulate growth, and provide sustainability, with particular focus on access to care. Professional psychiatric organizations should engage with emergency medicine professional associations to create joint workgroups to collaboratively address shared concerns regarding care. The newly formed Coalition on Psychiatric Emergencies, in which the American Psychiatric Association and American College of Emergency Physicians are members, is a great start. In addition, national organizations must engage with both government and insurers to solidify parity.

Specific emphasis should be placed on lobbying for fair reimbursement of services, including psychiatric emergency and inpatient services, as care places a financial strain on hospitals, thus providing a disincentive for hospitals to keep units open or add to existing services. Additionally, efforts must be made to reduce the burdensome precertification process, which is unique to psychiatry and adds to delays in admitting or transferring a patient from the ED. Finally, reducing or eliminating out-of-network hospitals for inpatient services will increase available options in some areas. One final consideration is to train more universally on crisis intervention modalities. Training could start as early as medical school, with advanced training in emergency medicine and psychiatry residency programs. This would better ensure that physicians have the appropriate tools to treat the person in a psychiatric crisis.

CONCLUSION

As ED visits for those with psychiatric illness continue to rise, collective thought and resources must be applied to reduce the boarding of these individuals in EDs. There are several changes that EDs can make to improve the care of patients who arrive at their doors, but ultimately community, state and national efforts will have to be focused on helping to divert patients to lower levels of care and to help ease transition of those in EDs and the inpatient setting back into the community.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Nicotine Gateway Effects on Adolescent Substance Use

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Section Editor: Tony Zitek, MD
Submission history: Submitted November 11, 2018; Revision received April 15, 2019; Accepted July 1, 2019
Electronically published August 20, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.41661

Given the rise in teenage use of electronic nicotine delivery systems ("vaping") in congruence with the increasing numbers of drug-related emergencies, it is critical to expand the knowledge of the physical and behavioral risks associated with developmental nicotine exposure. A further understanding of the molecular and neurochemical underpinnings of nicotine's gateway effects allows emergency clinicians to advise patients and families and adjust treatment accordingly, which may minimize the use of tobacco, nicotine, and future substances. Currently, the growing use of tobacco products and electronic cigarettes among teenagers represents a major public health concern. Adolescent exposure to tobacco or nicotine can lead to subsequent abuse of nicotine and other substances, which is known as the gateway hypothesis. Adolescence is a developmentally sensitive time period when risk-taking behaviors, such as sensation seeking and drug experimentation, often begin. These hallmark behaviors of adolescence are largely due to maturational changes in the brain. The developing brain is particularly vulnerable to the harmful effects of drugs of abuse, including tobacco and nicotine products, which activate nicotinic acetylcholine receptors (nAChRs). Disruption of nAChR development with early nicotine use may influence the function and pharmacology of the receptor subunits and alter the release of reward-related neurotransmitters, including acetylcholine, dopamine, GABA, serotonin, and glutamate. In this review, we emphasize that the effects of nicotine are highly dependent on timing of exposure, with a dynamic interaction of nAChRs with dopaminergic, endocannabinoid, and opioidergic systems to enhance general drug reward and reinforcement. We analyzed available literature regarding adolescent substance use and nicotine's impact on the developing brain and behavior using the electronic databases of PubMed and Google Scholar for articles published in English between January 1968 and November 2018. We present a large collection of clinical and preclinical evidence that adolescent nicotine exposure influences long-term molecular, biochemical, and functional changes in the brain that encourage subsequent drug abuse. [West J Emerg Med. 2019;20(5)696-709.]

INTRODUCTION

The growing use of tobacco and electronic nicotine delivery systems ("vaping") among teenagers represents a major public health concern. Smoking is not only the leading cause of preventable death worldwide, but epidemiological, clinical, and preclinical data have also shown that adolescent exposure to tobacco or nicotine can lead to subsequent abuse of nicotine and other substances.[1–19] This phenomenon is known as the gateway hypothesis.[10,20,21] Furthermore, adolescents are more likely to first experiment with combustible cigarettes and/or e-cigarettes than they are marijuana.[22,23] Sequence patterns of drug initiation were examined in a recent study (2015), which reported that 38.8 percent of adolescents initiate nicotine before alcohol and/or marijuana, while 21.3 percent use alcohol prior to nicotine and/or marijuana, and 8.6 percent use marijuana before nicotine and/or alcohol.[23]

Although previous reports highlight that the rates of cigarette smoking are decreasing in the United States (U.S.), from 20.9 percent in 2005 to 15.5 percent in 2016, current trends in teen use of electronic nicotine delivery systems (e.g., e-cigarettes, vaporizers, hookah pens) are rapidly increasing.[24–26] In particular, the rate of current e-cigarette use in high school students jumped from 1.5 percent in 2011

to 11.7 percent in 2017, then alarmingly to 20.8 percent in 2018.[24,27] Among middle school students, a rise of 48 percent in e-cigarette use has also been reported from 2017 to 2018. This translates to a massive surge of an additional 1.5 million youth having been exposed to e-cigarettes in the last year alone in the U.S. The youth are often attracted to e-cigarettes due to their flavoring, easy availability, and a lack of awareness of their harmful effects.[28,29] While e-cigarettes are marketed to aid in smoking cessation for adults, they have had inconsistent effects on cessation in adults and have been shown to promote smoking progression in the youth, with increased cigarette smoking in adolescents who had previously used e-cigarettes (19.1 percent) compared to those who had not (4.6 percent).[30,31] In this review, we present studies that support a causal role of adolescent nicotine exposure in maladaptive alterations in reward processing during and beyond adolescence, with molecular, neurochemical, and cognitive impacts on the brain that ultimately encourage subsequent drug use.

Adolescence is a period of transition characterized by significant hormonal, psychosocial, and neural changes in rodents (postnatal day (PND) 28-42) and humans (12-18 years of age).[32] Adolescence is a time of increased exploration and the development of social, emotional, and cognitive skills to prepare for independence of adulthood. However, adolescence is also associated with increased vulnerability to stress and risk-taking behaviors, such as sensation seeking and experimentation with recreational drugs.[33–35] These age-specific behaviors are largely due to maturational changes in the brain.

During this sensitive maturational period, the brain is particularly vulnerable to the harmful effects of drugs of abuse, including tobacco and nicotine products. Nicotine is the primary psychoactive constituent in tobacco products and binds to nicotinic acetylcholine receptors (nAChRs), which are pentameric ligand-gated ion channels composed of α and β subunits (α1-7, 9-10; β1-4). nAChRs are widely distributed throughout the human and rodent brain and periphery, and are critical in the processes of the neuromuscular junction, neurotransmitter release, brain maturation, reward processing, and cognition.[36–45] nAChRs are activated endogenously by acetylcholine or exogenously by nicotine, and are expressed by the majority of neuronal subtypes, including dopaminergic neurons, which facilitate drug intake and abuse.[46–49] Nicotine exposure during adolescence, in particular, disrupts the normal development and expression of neuronal nAChRs, ultimately altering the function and pharmacology of the receptor subunits and changing the release of dopamine, serotonin, GABA, glutamate, and other reward-related neurotransmitters.[50–52]

Many factors are recognized to contribute to the onset of teenage substance abuse, such as genetics, stress, and socioeconomic status.[53,54] While various mechanisms may impact substance abuse and addiction, this review focuses on the influence of developmental nicotine exposure on long-term changes in reward neural circuitry and subsequent drug use. We highlight findings from both human and rodent studies, as animal models provide insight into human brain maturation, physiology, and behavior.[32,55,56] We argue that the effects of nicotine are highly dependent on timing of exposure, and that nAChRs interact with other drug receptor systems to directly mediate reward and reinforcement.

Population Health Research Capsule

What do we already know about this issue?
Adolescent initiation of nicotine products is associated with future substance use, and teenage use of electronic nicotine devices ("vaping") is rapidly escalating.

What was the research question?
We performed a thorough review of the literature to characterize impacts of nicotine on the adolescent brain.

What was the major finding of the study?
Nicotine triggers changes in the adolescent brain that alter reward processing and encourage future drug use.

How does this improve population health?
Increasing collaboration, resources, and education about the risks of teen nicotine use may contribute to decreases in addiction and drug-related emergencies.

Clinical Implications

The escalation in teenage use of nicotine products prompts the need to raise awareness of the detrimental effects of developmental nicotine exposure. A more complete understanding of nicotine's gateway effects during adolescence is critical due to the extremely high and rising economic and societal costs, as well as deaths, associated with substance use. Estimates suggest that drug dependence in the U.S. is associated with over $700 billion in annual costs and more than 64,000 drug overdose deaths in 2016, which is nearly double what was observed the prior decade and continues to climb.[57–59] We provide evidence for the gateway hypothesis in an effort to build knowledge for Emergency Department clinicians and other healthcare professionals to exhaustively advise their patients and patients' caretakers. The depth of this understanding, specifically the molecular consequences of adolescent nicotine use, allows for individualized treatment

plans with a greater emphasis on medication interactions, care coordination, community resources, education, and advocacy. These clinical adjustments may contribute to decreases in addiction and drug-related emergencies.

METHODS

Prior to drafting this manuscript, the two authors independently evaluated and summarized research articles that addressed adolescent substance use and nicotine's impact on the developing brain and behavior. We conducted a comprehensive review of the literature using a two- to three-word combination of the following keywords: adolescence, substance use, nicotinic acetylcholine receptors, gateway, reward, smoking, tobacco, nicotine, alcohol, psychostimulant, cocaine, amphetamine, cannabis, opioids. We utilized the electronic databases of PubMed and Google Scholar for research articles published in English between January 1968 and November 2018. Articles were included in the review if they discussed nicotine exposure during adolescence, drug sequence patterns, or adolescent substance use. The references from relevant articles and websites of relevant organizations were also examined for other potential sources of information. Out of 80,000 initial search results, approximately 5,000 were reviewed as relevant and non-duplicate articles. To retain focus on adolescent initiation of nicotine products, studies related to maternal tobacco or nicotine exposure were excluded. Studies evaluating other interventions (i.e., medication, sleep, exercise) were also excluded to maintain focus on nicotine's effects on brain function and behavior. We grouped studies together according to their methodological similarities, so findings without substantial support or reproducibility (i.e., fewer than 5 comparable studies) were excluded. Following exclusion and careful analysis of studies based on key results, limitations, suitability of the methods to test the initial hypothesis, and quality and interpretation of the results obtained, 174 references were selected. The use of two reviewers and two extensive electronic databases allows for a widespread range of research articles, which maximizes scientific credibility and minimizes potential bias.

RESULTS

All Drugs of Abuse Share a Final Common Brain Pathway

Drugs of abuse provide rewarding, pleasurable feelings that contribute to its reinforcement (i.e. repeated use). Reward and reinforcing efficacy are measured in animals with drug self-administration on fixed and progressive ratio schedules of reinforcement, intracranial self-stimulation, oral intake, inhalation, and/or conditioned place preference. Although common drugs of abuse, like marijuana, cocaine, alcohol, and opioids, act on different neurotransmitter systems, they all exert their reinforcing effects via the mesolimbic pathway, a dopaminergic pathway that connects the ventral tegmental area to the nucleus accumbens.[60–66] The development, projections, and functions of this pathway are strongly influenced by acetylcholine, glutamate, serotonin, and GABA.[67–71] Dopamine release into the nucleus accumbens regulates motivation and desire for rewarding stimuli and facilitates reward prediction.[72,73] As nAChRs modulate dopamine release, the gateway hypothesis posits that adolescent nicotine exposure primes the brain's reward system to enhance the reinforcing efficacy of drugs of abuse.[74–77]

Nicotine Uniquely Activates the Adolescent Brain Reward System

Substantial epidemiological data suggest that teenagers are more vulnerable than adults to nicotine dependence following minimal tobacco exposure (fewer than seven cigarettes in one month), and individuals who begin smoking during adolescence are more likely to experience difficulty quitting than those who start as adults.[78–84] Indeed, 90 percent of adult smokers started before age 18.[34,59] Event-related functional neuroimaging studies in children, adolescents, and adults suggest that children and adolescents have over-reactive reward responses and improved task performance when earning rewards, suggesting enhanced engagement in behaviors that result in immediate gratification.[85] Such factors make adolescents more vulnerable to drug use and abuse.

Animal models allow for experimenter-controlled administration of nicotine and investigation of its direct consequences on the brain and behavior through neuroimaging, biochemical assays, and behavioral tests. Early adolescent rats exposed to intravenous nicotine levels equivalent to one to two cigarettes per day for four days (Figure 1) self-administer a greater amount of cocaine, methamphetamine, and alcohol compared to adolescent rats not exposed to nicotine, as well as compared to exposed and unexposed adults.[86,87] These data strongly suggest that adolescent nicotine use increases the reinforcing effects of other drugs. In addition, adolescent, but not adult, rodents exposed to nicotine display disruptions in hippocampal learning, long-lasting depressive phenotypes, changes in cocaine sensitivity and reward, enhanced drug-related learning, and deficits in impulse control, executive function, and cognition.[86,88–94] Improved drug-related learning following brief nicotine exposure during early adolescence is characterized by rapid initiation and cue association of cocaine and amphetamine self-administration, which is indicative of an addictive-like phenotype and is not observed in adolescent and adult controls or adults also pretreated with nicotine.[92,94] Furthermore, heightened depressive- and anxiety-like behaviors after 30 days of nicotine abstinence in mice exposed as adolescents, but not adults, indicate that nicotine exposure and withdrawal can have long-term effects on emotional and cognitive functioning, particularly when nicotine exposure occurs during adolescence.[89] The exact timing of exposure during adolescence is also significant, as nicotine's effects are far greater during early adolescence (PND 28-31 or 12-15 years) versus late adolescence (PND 38-41 or 16-18 years) or adulthood (PND 86-89).[86,95] Behavioral alterations brought on by developmental nicotine exposure are driven by molecular mechanisms, including epigenetic influences,

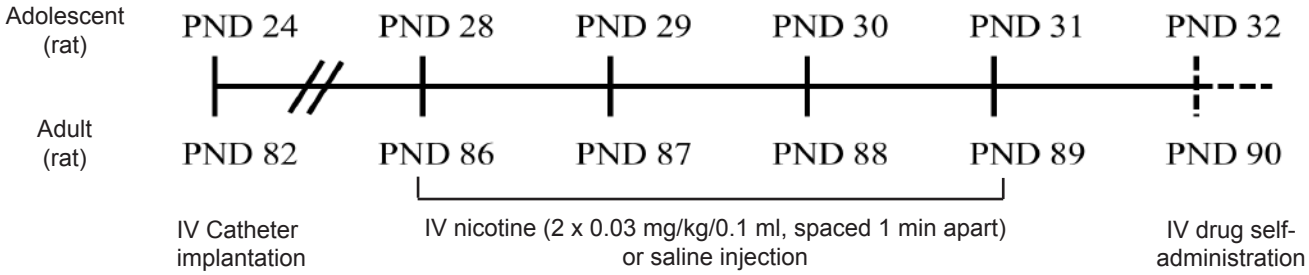

Figure 1. 4-day nicotine pretreatment paradigm in testing the nicotine gateway hypothesis in rats. Two intravenous nicotine (0.03 mg/kg/0.1 ml, equivalent to 1-2 cigarettes) or saline injections, spaced one minute apart, are administered daily for 4 consecutive days during early adolescence (PND 28-31) or adulthood (PND 86-89). Experimentation following nicotine pretreatment (dashed lines) varies upon the drug administered, duration of drug administration, and contingent or non-contingent injections. The daily nicotine dose yields peak serum levels of approximately 30 ng/ml in both adolescents in adults, which is well within the range of the average smoker. *PND,* postnatal day*; IV*, intravenous; *mg*, milligram; *kg*, kilogram; *ng*, nanogram; *ml*, milliliter.

synaptic activity, and receptor signaling and regulation.[8,96,97] Adolescent, but not adult, nicotine exposure in rodents results in the expression of distinct subunits of nAChRs (α5, α6, and β2) and persistent nAChR upregulation in the midbrain, cerebral cortex, and hippocampus.[98,99] Due to the role of nAChRs in neurotransmitter release and reward processing, alterations in their quantity and function influence reward behavior. In addition, brief nicotine exposure in early adolescent rats enhances cellular activity, dopamine D2 receptor signaling, and serotonin 5-HT receptor function in brain reward areas compared to adult rats also exposed to nicotine.[86,90,100] Moreover, chronic nicotine exposure during, but not after, adolescence alters gene expression in the ventral tegmental area and stimulates hyperresponsiveness of dopaminergic nerve terminals in the medial prefrontal cortex.[93,101,102] These nicotine-induced changes in reward-related neurotransmitters and brain regions during adolescence may contribute to alterations in reward regulation and behavior.

The changes in brain function and behavior from developmental nicotine exposure are long lasting and a consequence of manipulation of the brain's reward network, including the prefrontal cortex, nucleus accumbens, ventral tegmental area, hippocampus, and basolateral amygdala.[20] Specifically, adult rodents exposed to nicotine as adolescents show a persistent increase in deltaFosB in the nucleus accumbens, impaired GABA signaling in the ventral tegmental area, and changes in brain morphology and gene expression in reward regions.[93,101,103–105] Furthermore, adult rodents exposed to nicotine as adolescents have an increased preference for cocaine, amphetamine, opioids, and higher doses of nicotine.[103] The following section reviews in greater detail the impacts of adolescent versus adult nicotine exposure on subsequent drug use in animal models. Other drug-associated behaviors are beyond the scope of this review and will not be discussed.

Adolescent Nicotine Exposure Increases Alcohol Consumption

The developments of alcohol and tobacco use patterns are closely related among teenagers, but the order of progression is not universal among cultural and ethnic demographics.[106] Alcohol and nicotine products are more frequently co-abused than consumed separately, as a survey of high school seniors revealed that 88 percent of smokers were drinkers, while 55 percent of nonsmokers were drinkers.[107,108] However, tobacco use predicts subsequent alcohol use better than the reverse.[106] Individuals who initiate smoking before age 17 are at a higher risk of alcohol abuse and dependence than those who begin after 17.[109–111] These studies lead to the hypothesis that adolescent exposure to nicotine may lead to enhanced alcohol intake later in life.

Adolescent susceptibility to co-use of nicotine and alcohol is also observed in rodents, as concurrent self-administration of both drugs in adolescent, but not adult, rats is reinforcing and leads to an increase in subsequent oral alcohol intake.[112] Moreover, a different nicotine exposure paradigm promotes long-lasting increases in alcohol self-administration exclusively in nicotine-treated adolescents.[104] Nicotine exposure during adulthood can also change subsequent alcohol consumption, which indicates the influence of nicotine on alcohol reward and reinforcement; however, enhanced alcohol intake is more likely to occur if nicotine is administered prior to alcohol access.[113] These findings collectively indicate that nicotine exposure during adolescence enhances alcohol consumption more than if the same exposure occurs later in life.

Adolescent Nicotine Exposure Increases Psychostimulant Reinforcement and Reward

In humans, adolescent exposure to nicotine influences the likelihood of other psychostimulant use, including cocaine and methamphetamine.[3,5,8] Data from a 1994 National Household Survey on Drug Abuse report that individuals who smoked cigarettes before age 15 were up to 80 times more likely to use illegal drugs than those who did not, with cocaine being the most likely drug to be used among young cigarette smokers.[5] A separate study of a cohort representative of the U.S population revealed that the rate of cocaine dependence was highest among cocaine

users who initiated cocaine after having smoked cigarettes (20.2 percent), and the rate of dependence was much lower among those who initiated cocaine before smoking (6.3 percent).[8]

Preclinical studies also demonstrate associations between adolescent nicotine exposure and psychostimulant consumption. Chronic nicotine exposure differentially alters cocaine-induced locomotor activity and intravenous cocaine self-administration in adolescent versus adult rodents.[103,114–116] Adolescent rats exposed to nicotine become considerably more sensitized to the locomotor-activating effects of cocaine compared to non-exposed adolescents.[115] Nicotine exposure during adolescence, but not adulthood, also encourages increased self-administration of cocaine during adulthood, suggesting that nicotine use may carry a greater risk during adolescence than adulthood.[116] The effects of adolescent nicotine pretreatment on psychostimulant reinforcement and locomotor activity are mediated by nAChRs (α7 and α4β2) and serotonergic (5-HT1A) receptors.[86] In addition, chronic and sub-chronic nicotine-exposed adolescent rats experience greater preference for and self-administration of cocaine and methamphetamine versus saline-exposed rats.[86,87,117,118] Pre-adolescent nicotine exposure in rats also leads to increased cocaine-primed reinstatement, a model of relapse behavior.[119] In contrast, alcohol pre-exposure in rats does not influence subsequent cocaine self-administration or cocaine relapse behavior, highlighting the unique gateway effects of nicotine on psychostimulant use.[120]

Nicotine Interacts With the Endocannabinoid System

In addition to the enhanced use of alcohol and psychostimulants following early nicotine use, cigarette smoking in adolescents and young adults is associated with earlier onset of cannabis use, more frequent cannabis use, and a larger number of cannabis use disorder symptoms compared to those who did not smoke cigarettes.[9,121,122] Likewise, teens who use e-cigarettes or hookah are more than three times more likely to use marijuana, and cannabis users report that nicotine enhances the pleasurable effects of tetrahydrocannabinol (THC), the main psychoactive constituent of marijuana that exerts its effects via cannabinoid receptors.[19,123] The endocannabinoid system, which comprises cannabinoid receptors (CB1 and CB2) and endogenous ligands (anandamide and 2-Arachidonoylglycerol) throughout the central and peripheral nervous system, plays an important role in cognition, learning and memory, pain relief, emotion, stress, and reward processing.[124,125]

Although little research has been done on nAChRs interactions with THC specifically during adolescence, preclinical findings in adults suggest that cholinergic and endocannabinoid systems interact to modulate reward-related processes.[126–128] Selective antagonism of α7 nAChRs in rats blocks the discriminative effects of THC and reduces intravenous self-administration of a cannabinoid CB1 receptor agonist (WIN55,212-2).[129] This association appears to be bidirectional, as blockade of CB1 receptors reduces nicotine self-administration in rats.[130,131]

THC impacts adolescents and adults distinctively, where adolescent rats experience less of THC's anxiogenic, aversive, and locomotor-reducing effects than adult rats.[132] Nicotine also facilitates THC's hypothermic, antinociceptive, and hypolocomotive effects in mice.[126] Sub-chronic nicotine exposure in adolescent rats induces long-lasting effects in cannabinoid CB1 receptors, including increases in the hippocampus and decreases in the striatum.[133] The association between nicotine and cannabis use and the role of reward processing in both the cholinergic and endocannabinoid systems encourages the hypothesis that nicotine may encourage and perpetuate cannabis use.

Nicotine Interacts With the Opioidergic System

The endogenous opioid system is primarily involved in pain relief, reward processing, emotion, stress, and autonomic control, and consists of 3 families of receptors: mu, delta, and kappa.[134] Opioid receptors located in the brain and periphery are activated endogenously by enkephalins, dynorphins, endorphins, and endomorphins, as well as exogenously by opioids (e.g., heroin, morphine, oxycodone, fentanyl). Enkephalins, endorphins, endomorphins, and opioids act primarily through mu opioid receptors (MORs) to reduce pain perception, while dynorphins preferentially act at kappa opioid receptors (KORs) to regulate appetite, stress, and emotion. Mu and delta opioid receptors play a critical role in drug reward, whereas the KORs participate in drug aversion.[135–137]

Although opioid use has not been extensively evaluated during adolescence, an abundance of clinical and preclinical evidence suggests an important bidirectional relationship between nicotine use and opioid reward.[136] There is a significant overlap in the distribution of neuronal nAChRs and opioid receptors. Activation of nAChRs can influence excitability of opioid-containing neurons, and nicotine-induced dopamine release in the nucleus accumbens is dependent on activation of MORs in the ventral tegmental area.[138–140] Furthermore, nicotine induces a release of endogenous opioids in the brain, and repeated exposure to nicotine can alter expression and/or functioning of opioid receptors.[141–144]

Perhaps unsurprisingly, given the significant overlap of cholinergic and opioidergic systems, clinical data show that treatment with naloxone and naltrexone, both opioid receptor antagonists, reduces tobacco smoking and craving for tobacco smoke.[145,146] In addition, opioid-dependent smokers present with more severe nicotine dependence, respond poorly to smoking cessation medications, and may have a higher risk of relapse compared to non-opioid dependent smokers.[147–150]

The relationship between nicotine and the opioidergic system is similarly substantial in preclinical studies, which is important given the roles of both systems in reward processing. Early adolescent nicotine exposure in mice enhances subsequent morphine reward.[151] In addition, blocking nicotinic receptors reduces rewarding effects of morphine, and activation of MORs decreases nicotine withdrawal symptoms.[152–155] MOR antagonists increase somatic withdrawal symptoms and

aversion in nicotine-dependent mice and rats, and decrease nicotine self-administration, nicotine preference, and cue-induced reinstatement of nicotine seeking.[154,156–160] However, a small number of conflicting studies report no significant differences in nicotine reward, self-administration, or withdrawal following administration of a MOR antagonist, possibly as a result of differences in route of administration, dose, duration, or pharmacodynamics of the antagonist used.[160–162] Moreover, morphine exhibits significant functional interactions with nAChRs.[163] Chronic nicotine treatment in mice enhances the effect of morphine on striatal dopaminergic pathways, thereby influencing locomotor activity and reinforcement.[164]

Although there are minimal data on nicotine and opioid interactions during adolescence, increasing evidence supports a role of the KOR system in modulating nicotine-associated behaviors. Rodent studies suggest that teen susceptibility to nicotine use is likely due to adolescents finding nicotine more rewarding and less aversive than adults.[52,165–171] These differences in sensitivity to nicotine reward and aversion may be due, in part, to the KOR system, as activation of KORs increases aversive effects and withdrawal signs of nicotine in adult rodents, but not adolescents.[172–174] Furthermore, KOR antagonists increase concurrent nicotine and alcohol self-administration in adult, but not adolescent, male rats.[112] Given the interactions between the cholinergic and opioidergic systems in reward regulation and the alarming increases in opioid-related deaths, it is important to recognize and understand risk factors of opioid addiction, including adolescent nicotine exposure.

CONCLUSION

We present epidemiological and clinical findings supporting the gateway hypothesis (Table 1), and emphasize that early adolescent nicotine exposure in various rodent models increases the acquisition and intake of nicotine, alcohol, cocaine, and methamphetamine; co-use of nicotine and alcohol; and the rewarding effects of nicotine, cocaine, methamphetamine, and opioids (Table 2). Although thousands of constituents make up combustible cigarettes, the animal studies highlighted in this review investigate the effects of isolated nicotine, which is more translationally relevant to electronic cigarette use than tobacco/cigarette smoking. This review emphasizes the emerging theme that nicotine hijacks the brain's reward pathway, particularly during adolescence when the brain is rapidly maturing, by inducing long-term changes in brain chemistry and function.

Nicotine interacts with other neurotransmitter systems and as a result increases the rewarding effects of other drugs by enhanced activation of reward circuitry. Developing brains are incredibly susceptible to long-lasting changes from perturbations during maturation, leading to behavioral changes that continue into adulthood. The prevalence of nicotine use among adolescents and the extensive interactions between nicotinic receptors and drugs of abuse highlight the critical need to better understand how nicotine modulates long-term consequences on brain and behavior related to addiction vulnerability.

This comprehensive review was performed to provide insight into how teenage experimentation with nicotine can induce drastic, ongoing consequences on reward and reinforcement of other drugs of abuse. Alterations in nicotinic acetylcholine receptors are only part of what influence adolescent substance abuse, and the reasons why adolescents decide to use tobacco products and/or nicotine delivery devices need to be further studied. Recognizing adolescent nicotine use as a possible predisposition to addiction to nicotine itself or other substances may decrease illicit drug experimentation and the incidence of drug addiction. Thus, healthcare professionals should take caution when dealing with adolescents with a history of e-cigarette use and continue to inform about its risks. Given the biochemical adaptations as a consequence of adolescent nicotine exposure, physicians may take an individualized approach to treatment and provide additional resources for patients and their families. This increased education and advocacy may improve care coordination and lead to greater adherence to a discharge plan and improved clinical outcomes. Regulatory agencies should continue to establish age limits on the purchase of nicotine products, and increase education and awareness of the risks of smoking and/or vaping during adolescence.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. This work was supported by the Tobacco Related Disease Research Program grant 22RT-0103A (SL), a Brain and Behavior Research Foundation Grant 21517 (SL), University of California, Irvine, School of Medicine start up fund (SL), Institute for Clinical and Translational Science Pilot Studies Program (NIH/NCATS) (SL), University of California, Irvine, Helping End Addiction Long-term (HEAL) Initiative Opioid-Related Pilot Studies Program from the Institute for Clinical and Translational Science (ICTS), School of Medicine (SOM), Department of Medicine, and Department of Anesthesiology & Perioperative Care (SL), and the University of California, Irvine, Department of Emergency Medicine Pilot Award (SL). There are no other conflicts of interest or sources of funding to declare.

Table 1. Summary of epidemiological and clinical findings supporting the gateway hypothesis. Surveys of adolescents and/or young adults were conducted to assess gateway effects of nicotine on subsequent drug use. Details of these selected epidemiological and clinical surveys and findings are highlighted, including age, data source, data analysis, and main observation(s).

Age	Data source and analysis	Main observation(s)	Reference(s)
24-25 years (follow-up of former adolescents aged 15-16 years)	Longitudinal cohort of former New York State high school students, followed from grades 10 and 11 (ages 15.7-34.2). Detailed monthly drug use histories were obtained. The following sequence of progression was tested: alcohol, cigarettes, marijuana, other illicit drugs, and prescribed psychoactive drugs. In addition, months of use and non-use of cigarettes and cocaine were identified.	**Sequence pattern:** Cigarettes preceded marijuana use with or without initial alcohol use among women. However, in men, alcohol consistently preceded marijuana use even in the absence of initial cigarette use. Cigarettes preceded other illicit drugs among women, but not among men. **Cigarette and cocaine use:** Most cocaine users smoked cigarettes before they started using cocaine. In addition, most cocaine users started using cocaine while they were actively smoking cigarettes (i.e., within the same month).	3,5
11-16 years	Subjects were sampled from eight public schools in Milwaukee, Wisconsin. The subjects were interviewed twice, first during 1979-80 and again during 1981-82. Eighty-nine percent of those interviewed initially were re-interviewed two years later.	Cigarette use fell on a cumulative (Guttman) scale of use with other drugs (e.g., marijuana, beer, liquor, stimulants, depressants). Having tried substances lower on the Guttman scale made one significantly more likely to be using substances higher on the scale two years later. Use of cigarettes during middle or early high school significantly increased the likelihood that the subject would be using other drugs (e.g., beer, marijuana) two years later.	4
Years 12-15, 16-17, 18-25, 26-34, 35-49, 50 or over	1994 National Household Survey on Drug Abuse. Data were analyzed to clarify whether cigarette smoking has any effect on the initiation of illegal drug use.	Individuals who had smoked cigarettes were far more likely to use marijuana, cocaine, heroin, and/or crack. Those who smoked cigarettes before age 15 were up to 80 times more likely to use illegal drugs than those who did not. Cocaine was the drug most likely to be used among young cigarette smokers.	5
16-34 years	National Epidemiological Study of Alcohol Related Consequences, a cohort representative of the U.S. population. The rates of lifetime cocaine dependence were compared among three groups: 1) those who had started to use cocaine after they had started to smoke and before they had stopped smoking, 2) those who had started cocaine use before beginning to smoke; and 3) those who had ever smoked 0-100 cigarettes.	The rate of cocaine dependence was the highest among cocaine users who initiated cocaine after having smoked cigarettes. The rates of dependence were much lower among those who initiated cocaine before smoking or who had ever smoked 0-100 cigarettes.	8
11-20 years	National Longitudinal Study of Adolescent to Adult health data spanning a 14-year period. The relationship between gateway drugs during 11-20 years of age and drug use in adulthood was analyzed using generalized estimating equation regression models.	Exposure to marijuana and illegal substances during young adulthood was positively associated with illegal substance and cocaine use. Interactions between the gateway drugs and reporting high depressive symptoms in adolescence or adulthood were associated with increased use of marijuana, illegal drugs, and cocaine in early or young adulthood.	14
14-30 years	Systematic review and meta-analysis of longitudinal studies that assessed initial use of e-cigarettes and subsequent cigarette smoking. Study selection: longitudinal studies reporting odds ratios for cigarette smoking initiation associated with ever use of e-cigarettes or past 30-day cigarette smoking associated with past 30-day e-cigarette use.	E-cigarette use was associated with greater risk for subsequent initiation of cigarette smoking and past 30-day cigarette smoking.	17

Table 1. Continued.

14-16 years	Subjects were sampled from 10 public schools in Los Angeles, California. Students completed surveys at baseline (grade 9) and at a 24-month follow-up (grade 11). Associations of baseline e-cigarette, hookah, or combustible cigarette use with ever marijuana use (initiation), current marijuana use (past 30 days), and current dual use of marijuana and tobacco products were examined at the 24-month follow-up.	High schoolers who used e-cigarettes or hookah at baseline compared with those who did not were more likely to report initiation and current use of marijuana as well as dual use of tobacco and marijuana. E-cigarette and hookah use at age 14 years was associated with a 3.6- to 4-fold increase in the odds of initiating and currently using marijuana two years later. The use of e-cigarettes, hookah, and combustible cigarettes in early adolescence more than doubled the odds of currently using both tobacco and marijuana by mid-adolescence.	19

Table 2. Summary of preclinical studies supporting the gateway hypothesis. Rodent studies highlight nicotine pretreatment paradigms and subsequent observations, including nicotine treatment doses, duration of treatment, species used, age of exposure, behavior tests, and main observation(s).

Nicotine dose, route of administration, and duration	Species and age of nicotine exposure	Behavior test(s)	Main observation(s)	Reference
60 µg/kg, IV, 4 days	Sprague Dawley rats, PND 28-32 vs. PND 86-90	IV self-administration of cocaine (0.5 mg/kg/inj), methamphetamine (0.02 mg/kg/inj), or ethanol (1 mg/kg/inj), 1 day each	Adolescent rats pretreated with nicotine had increased initial acquisition of cocaine, methamphetamine, and ethanol compared to saline-treated adolescents and both saline- and nicotine-treated adults.	86
0.03 mg/kg/0.1 ml, IV, 2/daily for 4 days	Sprague Dawley rats, PND 28-32 vs. PND 86-90	IV self-administration of cocaine (200 or 500 µg/kg/inj), 5 days	Adolescent rats pretreated with nicotine had greater reinforced responding for cocaine compared to saline controls and adults.	87
0.4 mg/kg/day, IP, 10 days	Sprague Dawley rats, PND 34-43 vs. PND 60-69	IV self-administration of nicotine (0.04 mg/kg/inj), 15 days	Animals exposed to nicotine during periadolescence self-administered more nicotine than vehicle-exposed animals and animals exposed during postadolescence.	99
0.1, 0.5, or 1 mg/kg, SC, 2/daily for either 1 (acute) or 7 (repeated) days	ICR (CD-1) mice, PND 28-34 vs. PND 50-56	CPP for cocaine (1, 5, or 10 mg/kg, i.p.), morphine (5 mg/kg, s.c.), and amphetamine (0.2 mg/kg, s.c.,), 3 days conditioning	Adults exposed to nicotine during early but not late adolescence had increased CPP for cocaine, morphine, and amphetamine.	103
0.5 mg/kg, SC, 2/daily, 7 days	ICR mice, PND 24-30	Locomotor activity	Adults exposed to nicotine during early adolescence had enhanced cocaine-induced locomotor sensitization compared to saline-treated animals.	103
0.4 mg/kg, IP, 14 days	Long-Evans rats, PND 28-42	Operant ethanol self-administration: 8-day ethanol fading procedure (2-8% v/v)	Adults exposed to nicotine during adolescence had increased ethanol self-administration and altered GABA transmission and chloride homeostasis in the ventral tegmental area compared to adolescent and adult saline exposure and adult nicotine exposure.	104

Table 2. Continued.

0.1, 0.2, 0.4, 0.8 mg/kg, SC, 10 days	Wistar rats, 150 grams (age not specified)	Operant ethanol self-administration (12% v/v)	Nicotine pretreatment at a higher dose initially suppressed alcohol consumption but stimulated alcohol consumption on repeated treatment.	113
0.4 mg/kg, IP, 7 days	Sprague-Dawley rats, ~PND 30-37 vs. ~PND 60-67 (based on body weight)	Locomotor activity	Nicotine increased locomotor activity in all animals. Adolescent rats pretreated with nicotine had sensitization to nicotine-induced repetitive motion over the 7-day nicotine treatment period. Adolescent, but not adult, rats had increased amounts of cocaine-induced repetitive motion after nicotine pretreatment.	114
0.4 mg/kg, IP, 7 days	Sprague Dawley rats, ~PND 30-37 vs. ~PND 60-67 (based on body weight)	Locomotor activity, IV self-administration of cocaine (descending doses of 1.0, 0.5, 0.25, 0.125, 0.06 mg/kg/inj)	Adult rats exposed to nicotine during early adolescence were sensitized to the locomotor-activating effects of cocaine and self-administered a greater number of cocaine infusions than adolescent rats pretreated with vehicle.	116
0.4 mg/kg, IP, 10 days	Sprague Dawley rats, PND 35-44	CPP for cocaine (1 or 3 mg/kg, IP), 12 days alternating cocaine and vehicle	Adult rats that received nicotine treatment during adolescence had enhanced preference for cocaine.	117
0.16 or 0.64 mg/kg, SC, 16 days	Sprague Dawley rats, PND 35-50	IV self-administration of methamphetamine (0.05 mg/kg/inj); methamphetamine-primed reinstatement (1 mg/kg, IP)	Nicotine-exposed versus saline-exposed rats obtained more methamphetamine infusions. The high dose of nicotine had no effect on methamphetamine intake and neither nicotine dose altered methamphetamine-primed reinstatement.	118
0.1 or 0.5 mg/kg, SC, 2/daily, 7 days	ICR mice, PND 28-34 vs. PND 50-57 vs. PND 70-77	CPP for cocaine, morphine, or amphetamine	Mice treated with nicotine during early adolescence, but not late adolescence or adulthood, showed an increase in CPP for cocaine, morphine, and amphetamine later in adulthood.	151

PND, postnatal day; *IP*, intraperitoneal, *IV*, intravenous, *SC*, subcutaneous; *Inj*, injection, *CPP*, conditioned place preference; *μg*, microgram; *kg*, kilogram; *ml*, milligram.

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Examining the Effect of the Affordable Care Act on Two Illinois Emergency Departments

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Section Editor: Mark I. Langdorf, MD, MHPE
Submission history: Submitted December 10, 2018; Revision received June 6, 2019; Accepted June 8, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.6.41943

Introduction: The emergency department (ED) has long served as a safety net for the uninsured and those with limited access to routine healthcare. This study aimed to compare the characteristics and severity of ED visits in an Illinois academic medical center (AMC) and community hospital (CH) of a single health system before and after the implementation of the Affordable Care Act (ACA).

Methods: This was a retrospective record review of 357,764 ED visits from January 1, 2011– December 31, 2016, of which 74% were at the AMC and 26% at the CH. We assessed the severity of ED visits by applying the previously validated Ballard algorithm, which classifies ED visits as non-emergent, intermediate, or emergent. Descriptive analyses were conducted to compare the characteristics of ED visits before and after the implementation of the ACA. We conducted multilevel logistic regression analysis to examine the odds of non-emergent compared to intermediate/emergent ED visits by the ACA implementation status controlling for patient demographic characteristics, insurance status, and multiple visits per patient.

Results: ED visits for patients with Medicaid or other governmental coverages increased in the post-ACA compared to pre-ACA period (Pre: 33.2 % vs Post: 38.3% at the AMC, and Pre: 29.7% vs Post: 35.1% at the CH). A statistically significant decrease in ED visits for uninsured patients was observed at the AMC and CH in the post-ACA period compared to the pre-ACA period (Pre: 12.1% vs Post: 6.4%, and Pre: 13.9% vs Post: 9.8%, respectively). Results from the regression analysis showed a significant decreased odds of non-emergent vs intermediate/emergent ED visits during the post-ACA period compared to the pre-ACA period at the AMC (odds ratio [OR] 0.68; confidence interval [CI], 0.66-0.70). However, an increased odds of non-emergent vs. intermediate/emergent ED visits was observed at the CH (OR 1.09; CI, 1.04-1.14).

Conclusion: Similar to other Medicaid expansion states, ED utilization for uninsured patients decreased at both the AMC and the CH in the post-ACA period. While Medicaid visits for children < 18 years declined in the post-ACA period, it increased for ages 21 to 65 years of age. Contrary to our hypothesis, the severity of emergent ED visits increased in the post-ACA period but not at the CH. [West J Emerg Med. 2019;20(5)710-716.]

INTRODUCTION

The emergency department (ED) has long served as a safety net for the uninsured and those with limited access to routine healthcare. In recent years, ED crowding has worsened as patients who lack timely access to primary care have used the ED for non-emergent conditions. Inappropriate ED utilization can result in unnecessary testing, procedures, and admissions, all of which may contribute to rising healthcare

costs. The Affordable Care Act (ACA) of 2010 aimed to improve access to primary care providers for non-emergent complaints by providing expanded insurance coverage options. In 2013, Illinois opted to expand Medicaid to low-income adults resulting in a net increase in Medicaid coverage of more than 486,000 individuals in the first three years after implementation of the ACA.[1,2] Despite these efforts, studies measuring ED utilization before and after the enactment of the ACA have yielded mixed results.[3-5] Estimates of the effect of health insurance coverage on ED visits is a complex relationship that must be factored with out-of-pocket expenses to patients and access to alternative sources of healthcare, as well as reimbursement to primary care providers. Economic theory suggests that expanding access to health insurance could either increase or reduce ED use.[6]

Prior to the implementation of the ACA, an independently validated ED algorithm that classifies ED visits according to the severity of the visit was created to analyze and predict ED utilization patterns.[7,8] Applying the Ballard algorithm to analyze patterns in ED utilization before and after the ACA implementation could enhance the growing body of literature about understanding the impact of the ACA implementation. Results may guide future health policy legislation regarding strategies for alternative healthcare utilization, payor options, market place directions, and resource allocation.

This retrospective study compared the characteristics and severity of a single, suburban Illinois health system's ED visits. We assessed the severity of ED visits by applying the Ballard algorithm, which classifies ED visits to non-emergent, intermediate, and emergent. We hypothesized that similar to other Medicaid expansion states, the EDs would see an increase in the percentage of ED patients who were insured after ACA implementation but that the severity of ED visits would not be impacted as emergent conditions were likely still to require ED care. The primary outcome variable in this study was the severity of ED visits relative to implementation of the ACA. Secondary outcome variables included the characteristics of patients and ED visits.

Population Health Research Capsule

What do we already know about this issue?
After Affordable Care Act implementation in Medicaid expansion states such as Illinois, emergency departments (EDs) experienced an increase in visits, primarily for insured patients.

What was the research question?
This study examined the severity of ED visits of a single health system by application of the Billings-Ballard algorithm.

What was the major finding of the study?
Visit increases at the academic medical center were classified as emergent compared with non-emergent at the community hospital.

How does this improve population health?
Variances in ED use across a single health system highlight the need to develop strategies for non-emergent patient access and alternative resources for emergent patients.

METHODS

We performed a retrospective record review of ED visits from a single health system's electronic health record (EHR). The study comprised a Level 1 academic medical center (AMC) in Maywood, IL, and a Level 2 community hospital (CH) four miles away in Melrose Park, IL, before and after the implementation of the ACA. Neither ED has an affiliated emergency medicine residency, but the AMC supports residents from other core specialties. We electronically extracted the data from the clinical data warehouse, where data from the EHR resides and is refreshed nightly. The variables definition sheet was prepared by the investigators and provided to the health system's senior programmer, who performed the data extractions. The extracted data was reviewed by the study investigators for any inconsistencies and validated by chart reviews by the emergency physician on the team in a random sample of ED visits (~50 patients) to validate that the data pulled electronically met the variables definitions. The timeline of the AMC data query was from January 1, 2011–December 31, 2016, and the CH from January 1, 2013–December 31, 2016. The CH's query was limited to the period when electronic data from the EHR was available. A pre-ACA period was defined from January 1, 2011–December 31, 2013, and a post-ACA period from April 1, 2014–December 31, 2016. We excluded ED visits from January 1, 2014–March 31, 2014, from this study to avoid uncertainties around the ACA open enrollment period. We also excluded from the analysis all visits in which patients left without being seen. The study was reviewed and approved by the health system's institutional review board.

We used the Ballard algorithm to classify the ED visits into emergent, non-emergent, or intermediate based on the discharging *International Classification of Diseases*, 9th and 10th revisions (ICD-9/10) diagnosis codes. The unclassified category in this study included uncommon diagnoses and diagnoses of mental health, injuries, and substance and alcohol abuse. The focus of the Billings and later revised Ballard algorithms were to identify ED visits that could have been preventable by appropriate primary care. The original Billings algorithm assigned the probability that each ED visit ICD-

9/10 diagnosis code fell into one of four severity categories: non-emergent (NE), primary care treatable emergency (PCT), a preventable or avoidable emergency not treatable in an office visit (EPA), and an emergency that is not preventable or avoidable (ENPA). The algorithm excludes uncommon diagnoses and treats mental health, injuries, and substance and alcohol abuse diagnosis separately.

In the revised Ballard algorithm, the probabilities derived from the ICD-9/10 diagnosis code were used to classify each visit as non-emergent or emergent using the dominant probability, or intermediate when there was 50% probability of being both emergent and non-emergent. NE and PCT were considered non-emergent, and EPA and ENPA were considered emergent. Each ED visit was then classified as emergent or non-emergent using the classification of the most emergent diagnosis. For example, in the Ballard algorithm, infectious colitis has 100% probability of being non-emergent. Cardiac dysrhythmia has 13% probability of being non-emergent and 88% probability of being emergent; therefore, it is classified as emergent. Hypertensive chronic kidney disease has 79% probability of being non-emergent and 21% probability of being emergent; therefore, it is classified as non-emergent. [7,8]

We conducted descriptive univariate analyses for proportions and bivariate comparisons using the chi-squared test for categorical variables and conducted the t-test for continuous variables to compare the characteristics of ED visits before and after ACA implementation. The severity of visits was compared before and after implementation of the ACA by location of visits. We conducted multilevel logistic regression analysis to examine the odds of non-emergent ED visit compared to intermediate/emergent ED visits by the ACA implementation status, with unclassified ED visits by the Ballard algorithm excluded from the regression analyses. The analyses controlled for patient demographic characteristics and insurance status. Multiple visits per patient were adjusted in the regression analysis with a random effect term. All statistical tests were two-sided and a $P<0.05$ was considered statistically significant. We conducted all analyses using the Stata 15.1 (College Station, TX) statistical software.

RESULTS

There were 357,764 ED visits during the study period, of which 74% were at the AMC and 26% at the CH. Patients' demographic characteristics and insurance status differed significantly between pre- and post-ACA periods at the AMC and CH. When compared to the pre-ACA period, AMC and CH ED visits for children < 18 years decreased in the post-ACA period (Pre: 24.7% vs Post: 22.3%, and Pre: 17.5% vs. Post: 16.0%, respectively), while AMC and the CH ED visits for ages 40 to 64.9 years increased post-ACA (Pre: 28.9% vs Post: 30.9%, and Pre: 28.7% vs Post: 29.5%, respectively). AMC ED visits for Black patients decreased post-ACA (Pre: 39.8% vs Post: 36.2%), while visits for Hispanic patients increased (Pre: 21.7% vs Post: 24.8%). AMC and CH ED visits for patients with Medicaid or other governmental coverages increased in the post-ACA (Pre: 33.2% vs Post: 38.3%, and Pre: 29.7% vs Post: 35.1%, respectively). Uninsured patients accounted for a statistically significant decrease in AMC and CH ED visits in the post-ACA period (Pre: 12.1% vs Post: 6.4%, and Pre: 13.9% vs. Post: 9.8%, respectively).

Also compared to pre-ACA, at the AMC the proportion of Medicaid ED visits for children younger than 18 years decreased significantly post-ACA (Pre: 51.3% vs Post: 39.1%). Conversely, the percentage of AMC ED Medicaid visits in the older age brackets all increased in the post-ACA period, from Pre: 7.5% vs Post: 8.8% (21 to 25.9 years), Pre: 18.1% vs Post: 21.0% (26 to < 39.9 years) ,and Pre: 16.8% vs Post: 24.5% (40 < 65 years).

The mean number of ED visits per patient declined at the AMC (Pre: 1.41 vs Post: 1.35) and at the CH (Pre: 1.38 vs. Post: 1.36) from the pre- compared to post-ACA period (Table 1). At the AMC, compared to the pre-ACA period there was a statistically significant increase in the ED visits that resulted in hospitalization during post-ACA (Pre: 32.1 % vs Post: 35.0%). At the CH, compared with the pre-ACA period, the post-ACA period saw a statistically significant decline in the ED visits that resulted in hospitalization (Pre: 29.4% vs Post: 28.2%) (Table 2). Readmissions within 48 hours and one week were not statistically different from pre- to post-ACA period at the AMC and CH.

During the study period, the distribution of the severity of AMC ED visits for emergent and non-emergent visits varied significantly (Figure 1). Compared to pre-ACA, a higher percent of ED visits at the AMC were emergent post-ACA (Pre: 37.8% vs Post: 46.3%), while conversely there was a decline in the non-emergent visits (Pre: 42.4% vs Post: 38.5%). The CH did not experience similar changes in the categories of emergent and non-emergent visits.

Results from the regression analysis showed significantly decreased odds of non-emergent vs intermediate/emergent ED visits during the post-ACA period compared to the pre-ACA period at the AMC across all payor groups (odds ratio (OR) 0.68, confidence interval (CI), 0.66-0.70). However, an increased odds of non-emergent vs intermediate/emergent ED visits was observed at the CH (OR 1.09; CI, 1.04-1.14) (Table 3). Results were similar when the analysis was repeated for the odds of non-emergent vs emergent only, excluding intermediate ED visits from the analysis. Stratified regression analysis by insurance status showed similar results; however, notably, the odds of non-emergent visits increased significantly during post-ACA in Medicare and uninsured patients in the CH.

DISCUSSION

Recent studies have yielded mixed conclusions in evaluating changes in ED utilization following ACA implementation in Medicaid expansion states.[9-13] Several studies have shown no significant increase in ED visits, while

Table 1. Patient characteristics at a single, suburban health system emergency department before and after the implementation of the Affordable Care Act in Illinois (N=357,764; 2011-2016).

	Academic Medical Center			Community Hospital		
Patients characteristics	Pre-Affordable Care Act	Post-Affordable Care Act	p-value	Pre-Affordable Care Act	Post-Affordable Care Act	p-value
Number of visits[a]	143,372	120,881		23,253	70,258	
Gender			<0.001			0.2
Female (%)	53.8	53		55.9	55.4	
Male (%)	46.2	47.0		44.1	44.6	
Age (%)			<0.001			<0.001
< 18 years	24.7	22.3		17.5	16.0	
18 – 20.9 years	3.9	3.5		4.2	4.0	
21 – 25.9 years	7.2	7.1		7.8	8.0	
26 – 39.9 years	17.9	17.5		19.0	19.3	
40 – 64.9 years	28.9	30.9		28.7	29.5	
65 years and older	17.4	18.8		22.9	23.2	
Race (%)			<0.001			0.047
White	40.7	42.7		75.0	74.3	
Black	39.8	36.2		18.5	18.9	
Asian	1.1	1.5		1.2	1.4	
Other[b]	18.4	19.4		5.2	5.2	
Ethnicity[c](%)			<0.001			0.33
Non-Hispanic	78	74.4		64.2	63.9	
Hispanic	21.7	24.8		35.3	35.7	
Insurance Status(%)			<0.001			<0.001
Private	32.7	31.8		30.1	28.8	
Medicare	22.0	23.4		26.3	26.3	
Medicaid, other governmentally insured	33.2	38.5		29.7	35.1	
Uninsured	12.1	6.4		13.9	9.8	

[a]Visit numbers pre- and post-Affordable Care Act are not comparable due to different assessment periods.
[b]Other race categories include Alaska native, Native American, multiracial, Native Hawaiian, and other Pacific Islander.
[c]Column percents do not total 100% due to missing values in the ethnicity variable. Missing categories were excluded from the bivariate analysis reported in the table.

others (including studies in Illinois) demonstrated increased ED utilization following ACA implementation.[12,13] While there is a growing body of literature comparing ED volumes and payor mixes in the pre- and post-ACA periods, to our knowledge none have investigated changes in the severity of ED visits. In Illinois, over 600,000 people have enrolled in Medicaid since expansion in 2014, with Medicaid and the Children's Health Insurance Program now covering 2.9 of the 12.8 million citizens.[1] However, there is only one primary care physician (PCP) for every 1462 citizens, one of the lowest ratios nationally.[14] Although many patients gained insurance coverage as a result of the ACA, access to healthcare remains an obstacle. Many theorized that increasing insurance coverage without a significant increase in PCPs could overwhelm EDs with non-emergent visits in patients empowered by their new insurance status to seek medical care but unable to obtain timely, primary care appointments.

Given the inconsistencies in the literature, we sought to examine the severity of ED visits pre- and post-ACA implementation periods in an AMC and a CH located in a major urban area within a Medicaid expansion state. Similar to other studies, our results demonstrated that utilization for uninsured patients decreased at both the AMC and the CH in the post-ACA period. While Medicaid visits for children < 18 years declined in the post-ACA period, it increased for ages 21 to 65 years of age. Children's healthcare needs often involve wellness and routine immunizations not available in the ED setting. Insurance coverage may now have aligned children with a PCP for both wellness and other non-emergent needs. The increase

Table 2. The characteristics of emergency department visits before and after the implementation of the Affordable Care Act at a single, suburban health system in Illinois (N = 357,764; 2011-2016).

	Academic Medical Center			Community Hospital		
Characteristics of ED visits	Pre-Affordable Care Act	Post-Affordable Care Act	p-value	Pre-Affordable Care Act	Post-Affordable Care Act	p-value
Number of visits/patient/year (mean, SD)	1.41 (1.14)	1.35 (0.98)	<0.001	1.38 (0.95)	1.36 (0.92)	0.16
Readmissions (%)						
Within 48 hours	2.1	2.1	0.75	2.0	1.9	0.3
Within 1 week	5.2	5.0	0.013	4.7	4.7	0.9
Visit resulted in hospitalization (%)	32.1	35.0	<0.001	29.4	28.2	<0.001

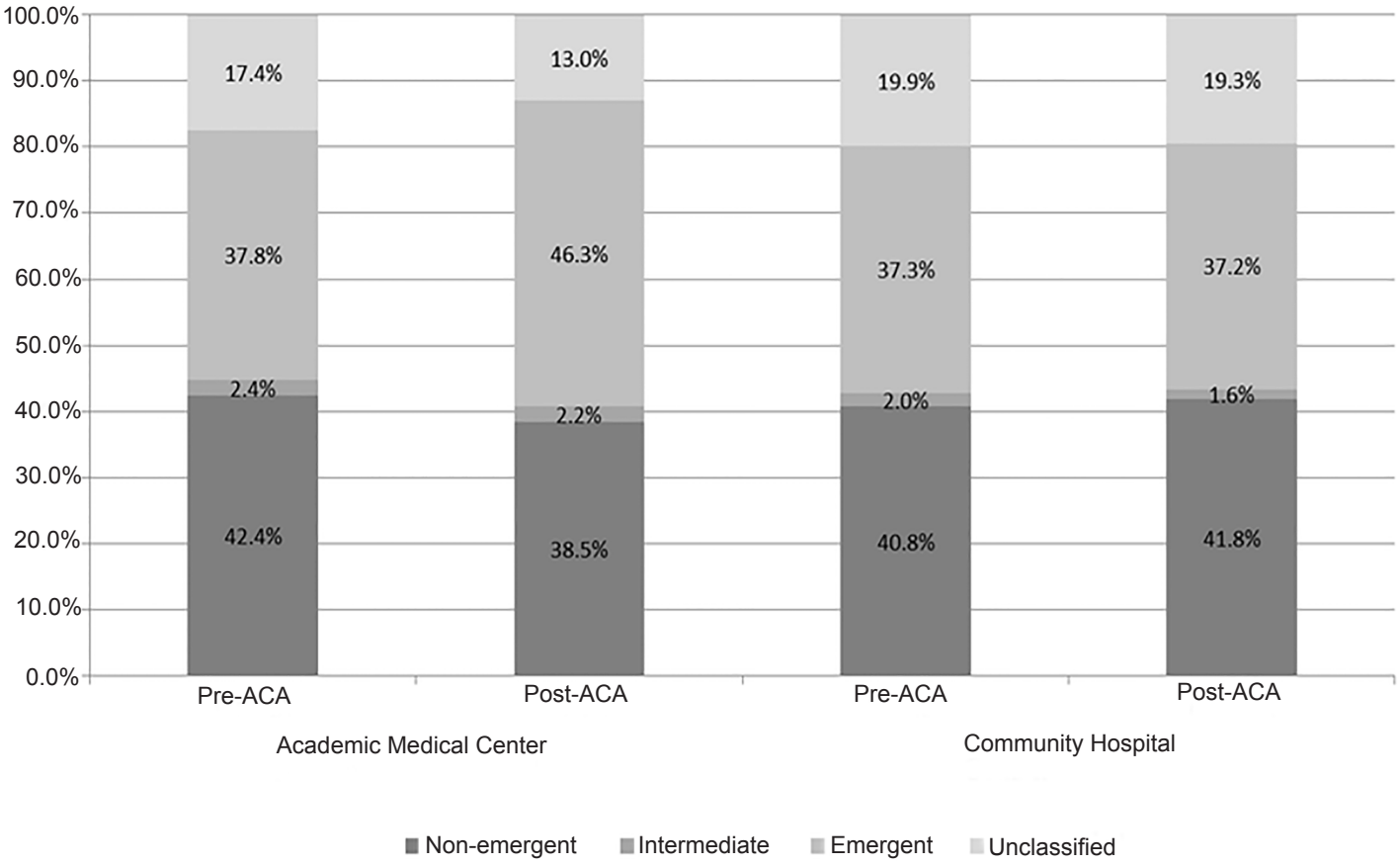

Figure 1. The severity of emergency department visits according to the Ballard algorithm.

in the proportion of ED visits for newly eligible Medicaid patients (21-65 years of age) observed in this study may reflect the literature regarding barriers to regular primary care in this population and the use of the ED as the safety net. While one major aim of the ACA was to expand the use of primary care, this goal may not have been realized in the study's population and timeframe.[15]

This study employed the Billings-Ballard algorithm to investigate the severity of ED visits pre- and post-ACA implementation across all age ranges. The severity of ED visits in this study varied by ACA implementation. The decrease in non-emergency visits to this single AMC ED post-implementation would align with the goals of the ACA to decrease potentially unnecessary, non-emergent visit types to the ED. Emergent visits increased post ACA, as did hospitalizations at the AMC. Severity of visits at the CH ED post ACA was not

Table 3. The odds of non-emergent emergency department (ED) visits compared to intermediate and/or emergent ED visits by Affordable Care Act (ACA) implementation status where the pre-ACA period is "referent" category and stratified by insurance status (N = 298,947).

	Odds ratio (OR) of non-emergent vs intermediate and emergent (N= 298,947) OR (95% CI)	Odds ratio of non-emergent vs emergent (N=291,222, excluding intermediate ED visits) OR (95% CI)
Academic Medical Center		
All ED visits	0.68 (0.66-0.70)**	0.66 (0.64-0.67)**
For privately insured	0.68 (0.65-0.71)**	0.66 (0.63-0.69)**
For Medicaid and other government-insured	0.71 (0.68-0.74)**	0.74 (0.71-0.77)**
Medicare	0.66 (0.63-0.70)**	0.65 (0.62-0.69)**
Uninsured or self-pay	0.65 (0.59-0.71)**	0.63 (0.57-0.69)**
Community Hospital		
All ED visits	1.09 (1.04-1.14)**	1.08 (1.03-1.13)**
For privately insured	1.05 (0.97-1.15)	1.04 (0.95-1.13)
For Medicaid and other government-insured	1.03 (0.95-1.13)	1.03 (0.94-1.13)
Medicare	1.11 (1.02-1.21)*	1.10 (1.01-1.20)*
Uninsured or self-pay	1.43 (1.23-1.66)**	1.41 (1.20-1.64)**

CI, confidence interval.
Pre-ACA period is the "referent" category. Analyses controlled for insurance status (in the all-ED visits model), age, gender, race, ethnicity and patient-random effects. ED visits were excluded from the analysis if they were unclassifed according to the Ballard algorithm and occurred during the study exclusion period. Missing categories were treated as separate categories.
*p<0.05; **p<0.001.

similarly impacted. On the contrary, at the CH, the post-ACA period saw increased odds of non-emergent visits and a statistically significant decline in the ED visits that resulted in hospitalization compared with pre ACA. This disparity in severity of visits across just one healthcare system's AMC and CH points to the still-incomplete understanding of how our patients use their insurance to access healthcare. Health system allocation of resources across hospitals, patients' perception regarding need for tertiary care, ED wait times, access to both urgent care and primary care, as well as emergency medical services, may all impact the differences in severity of ED visits between the ACA and the CH over time.

As healthcare systems are called upon to reduce unnecessary costs while still providing value, redirecting non-emergent ED care to less costly alternatives within the system will continue to be prioritized. If emergent visit types also represent high-risk, high-utilization patients, the system should prioritize these patients for care coordination. Incentivizing PCPs to see Medicaid patients in an ambulatory environment has shown to be impactful in improving access for non-emergent conditions in the past and should be investigated again.[16]

LIMITATIONS

This study analyzed the severity of visits at two Illinois EDs in a major urban area that may not be representative of trends in visits to other health systems' EDs across the state or country. The geographic span of the study's institutions include neighborhoods with high poverty levels, and thus our results may reflect the effects of the ACA for low-income individuals. Inclusion of both an urban academic medical center and a community hospital in the study may improve the generalizability of our findings. The unclassified category in our analysis was aligned with that of the Ballard algorithm, in addition to cases involving a primary diagnosis of injury, mental health conditions, alcohol or substance abuse; these may represent a not-insignificant burden of visits to any ED. The CH's data query was limited to the period when electronic data from the EHR was available at that site, in the beginning of January 2013. The expansion of the local, urgent care networks, as well as the primary care networks related to the AMC and CH, may have impacted ED utilization although neither was analyzed in this study.

CONCLUSION

In a Medicaid expansion state, the impact of the ACA on a single health system was not consistent across an academic health center and a community hospital. However, a consistent decrease in Medicaid ED visits was observed for children < 18 years and an increase for adults between 21-65 years of age. A larger proportion of ED visits to the AMCs were emergent in the post-ACA period, which was not observed at the CH.

Results from this study may impact the redesign of healthcare reimbursement and delivery systems with an emphasis on preventive and primary care, and an integrated care approach for avoiding preventable ED visits. Our results should not be interpreted for cost-containment measures by health insurers in penalizing patients for presenting to the ED with self-assessed symptoms that could have been serious and by avoiding the ED visit, detrimental to patients' health.[17,18]

ACKNOWLEDGEMENTS

The authors wish to thank the Informatics and Systems Development team and Ms. Susan Zelisko, Senior Program Analyst, at Loyola University Chicago, for their support in securing data for this study.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Case for Open Access and the Current Situation with the University of California and Elsevier

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Section Editor: Mark Langdorf, MD, MHPE
Submission history: Submitted July 22, 2019; Accepted July 22, 2019
Electronically published [date] (Add date right before publishing in Articles in Press)
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.44615
[West J Emerg Med. 2019;20(5)717-718.]

In my own words:

In recent months, the University of California has gained significant attention for taking a strong stance in support of open access publishing of UC research as it negotiates new agreements with major journal publishers. Cambridge University Press has agreed, enthusiastically, to partner with UC in piloting this new model while, thus far, UC's negotiations with Elsevier have resulted in a stalemate.

The University of California has a long history of supporting open access. The UC Academic Senate adopted an open access policy in 2013, with the goal of ensuring that future research articles authored by faculty at all 10 campuses of UC will be made available to the public at no charge. In 2015 the Presidential Open Access Policy expanded this stance to include all other authors who write scholarly articles while employed at the University of California.

As an academic librarian, my primary goal is to assist my community of faculty, students, researchers, and clinicians as they navigate the information life cycle, work to understand problems and create new knowledge. Open access is a business model that will ensure several outcomes in this regard. First, it allows the creators of information to maintain ownership of their most important asset, their intellectual property. Of equal importance, open access allows the public access to the information that they have paid to create. There is little research that does not have some form of public funding behind it, either explicitly through grants and other funding, or indirectly, through the labs, personnel, and other resources provided by state and federal funds. A third very important aspect of open access is that it provides a sustainable way for scholarly communication to take place.

This last point merits some amplification. I have been fortunate to have spent my career in well-supported, research-intensive institutions. I started my career after the severe budgetary challenges of the early 1990s, and when the 2008 financial crisis hit, the institution at which I worked had the political will and funding to protect library budgets. While there have been a few instances where licensing or other issues meant that we've been unable to provide access to a certain product, I have never had to decline a faculty or student request for information based on financial reasons. True, I have had to say "wait" – for the new fiscal year, for another license to expire, for special funding to be approved – but I have not had to say "never."

But outside this rarefied and privileged world, information seekers and information professionals have to make dire choices all the time. I believe one of the most important aspects of my job is insulating my community from that harsh reality; indeed, a librarian's job is to connect the users that we serve with all the resources that they need. Yet, for many libraries – as well as for many individuals and other organizations – the cost of accessing "pay-walled" articles, which still account for the vast majority of the scientific literature, is simply unaffordable.

While some might cynically ask why folks not directly engaged in the research enterprise might need access to certain highly technical content, or why it is so crucial that this content be openly available, there are two answers. First, as alluded to above, as taxpayers everyone contributes to creating it, so everyone should be able to read it. A second, more subtle answer is suggested by a caller to a National Public Radio program focused on the UC/Elsevier negotiations. The caller was a community physician and she lamented the fact that paywalls often kept her from content that would assist her in patient care and professional development. So, the conversation is a bit more nuanced in that regard: It's not just about "the average people on the street" but about the folks who need information to do their best to help them.

For all the rhetoric about "transformative" scholarly

communication in the University of California's negotiations with Elsevier, the propositions being raised by the University are fundamentally conservative. We want UC authors to determine where and how they will share the intellectual property that they create, including where they will publish, what they will read, and what roles they will play in the editorial process.

The last few weeks have provided great assurance that the University of California going forward will have agreements based on open access principles, including with Elsevier. Norway has reached an open access deal with Elsevier and the University has reached an open access deal with another important publisher, Cambridge University Press. In these models, which work on the principles of "pay to publish," costs are contained and risks mitigated for both institutions and publishers, which will create a sustainable and open scholarly ecosystem.

John Renaud is Associate University Librarian for Research Resources at the University of California, Irvine. The views expressed here are his own and do not represent the opinions of the University of California, Irvine, or the UC system.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

Single Versus Double Tourniquet Technique for Ultrasound-Guided Venous Catheter Placement

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Section Editor: Shane Summers, MD
Submission history: Submitted April 8, 2019; Revision received June 22, 2019; Accepted July 2, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.43362

Introduction: Peripheral, ultrasound-guided intravenous (IV) access occurs frequently in the emergency department, but certain populations present unique challenges for successfully completing this procedure. Prior research has demonstrated decreased compressibility under double tourniquet technique (DT) compared with single tourniquet (ST). We hypothesized that catheters inserted under DT method would have a higher first-stick success rate compared with those inserted under ST method.

Methods: We randomized 100 patients with a history of difficult IV access, as defined by past ultrasound IV, prior emergency visit with two or more attempts required for vascular access, history of IV drug abuse, history of end stage renal disease on hemodialysis or obesity, to ultrasound-guided IV placement under either DT or ST method. We measured the vein characteristics measured under ultrasound, and recorded the number of attempts and location of attempts at vascular access.

Results: Of an initial 100 patients enrolled, we analyzed a total of 99 with 48 placed under ST and 51 placed under DT. Attending physicians inserted 41.7% of ST and 41.2% of DT, with non-attending inserters (including residents, nurses, and technicians) inserted the remainder. First-stick success rate was observed at 64.3% in ST and 66.7% in DT (p=0.93). Attendings had an overall higher first-stick success rate (95.1%) compared to non-attending inserters (65.5%) (p=<0.001). The average vein depth measured in ST was 0.73 centimeters (cm) compared with 0.87 cm in DT (p=0.02).

Conclusion: DT technique did not produce a measureable increase in first-stick success rate compared to ST, including after adjusting for level of training of inserter. However, a significant difference in average vein depth between the study arms may have limited the reliability of our overall results. Future studies controlling for this variable may be required to more accurately compare these two techniques. [West J Emerg Med. 2019;20(5)719-725.]

INTRODUCTION

Peripheral intravenous (IV) access is one of the most common invasive procedures performed in emergency departments (ED) and is frequently required for diagnosis and treatment of patients with a wide spectrum of conditions. A certain subset of patients including those with obesity, a history of IV drug abuse, chronic diseases, and acute hypovolemia presents a particular challenge in establishing IV access, which would otherwise be a routine intervention.[1,2] Ultrasound-guided peripheral venous access (USGPIV) is an approach to establish IV access in patients with difficult vascular access (DVA),[3] which can successfully be used by both emergency physicians (EP) and support staff.[8-10]

Past studies of USGPIV have reflected that larger vessels

cannulate more easily.[11] Here we specifically explore the effect of the double tourniquet (DT) method on successful IV cannulation. This method was previously demonstrated to decrease vein compressibility.[12] While in the previous evaluation vein size and compressibility were measured, impact on successful insertion was not evaluated. The objective of this investigation was to test whether a DT placement enhances first-stick success with USGPIV cannulation compared to standard, single tourniquet (ST) placement.

Population Health Research Capsule

What do we already know about this issue?
Double tourniquet technique has demonstrated decreased vein compressibility as measured under ultrasound when performed in healthy volunteers.

What was the research question?
Does double tourniquet technique lead to improved ultrasound guided IV first stick success rate over single tourniquet?

What was the major finding of the study?
Double tourniquet technique did not demonstrate increased first stick success rate when compared to single tourniquet.

How does this improve population health?
Difficult IV access patients may benefit from ultrasound guided IV placement, but double tourniquet technique does not appear to improve success in placement.

METHODS

Study Design and Setting

This study was a prospective, randomized, comparative evaluation of single vs double tourniquet placement on first-stick, USGPIV cannulation success. It was approved by the institutional review board (IRB) at the home institution. We conducted the study in the ED of a suburban, academic teaching tertiary-care center with more than 130,000 visits per year. The IRB waived written informed consent for study participants and required that subjects be verbally consented. The sample size was based on enrollment feasibility and possibility of exploratory analyses; no prior power analysis was performed.

EPs (residents and attendings) and ED ancillary staff (nurses and technicians) who were proficient in USGPIV placement using single-user technique performed the US-guided peripheral IV insertion. We analyzed insertions under the grouping of attending physicians (42) vs a combination of resident physicians and ancillary staff (58). Departmental certification in US-guided vascular access involves attending a two-hour, vascular access didactic session followed by successful placement of US-guided IVs in the ED. The didactic session includes a discussion of relevant anatomy, insertion techniques, pitfalls, and training with the Blue Phantom 2 Vessel Ultrasound Training Block (CAE Healthcare, Sarasota, FL 34240). All inserters had at least one year of experience in this procedure. No specific training or refresher was offered prior to subject enrollment.

Selection of Participants

Research staff and investigators recruited a convenience sample of DVA patients presenting to the ED between June-August 2018. Investigators consented patients and provided an information sheet outlining the study protocol. Study participation was voluntary, and consent was obtained prior to enrollment. Post consent, patients were randomized using an envelope system of randomization to either ST or DT group. This was simple randomization done by the biostatistics department using a computerized system with a 1:1 ratio for each group. The investigator opened the envelope once the eligibility was confirmed and the patient was consented.

Patients eligible for the study had to be at least 18 years of age, had to have failed a blind IV attempt in the current department visit, and been identified as a DVA patient with at least one of the following:

1. History of IV drug use.
2. End stage renal disease on hemodialysis.
3. History of needing a rescue catheter such as US-guided IV, central venous catheter, or peripherally inserted central catheter on a previous hospitalization.
4. At least two, blind, unsuccessful attempts during present visit
5. Patient request of an ultrasound-guided IV without prompting.

Patients were excluded if they voluntarily withdrew from the investigation.

Assessment/Procedure

Patients randomized to the ST had a single device placed on the arm or forearm at the discretion of the inserter, and those randomized to a DT had the initial tourniquet placed followed by a second approximately 30 centimeters (cm) distal to the first (Figure 1). In both cases, vein diameter was measured both prior to and after placement of a tourniquet.

The investigators were trained to perform uniform bedside assessment of the venous system including measuring and saving vessel depth and diameter. The linear array transducer was used for all insertions, either a L12-4s Mindray M9 unit (Mindray North America, San Jose, CA) or a HFL38xp Sonosite X-Porte (FUJIFILM Sonosite, Inc, Bothell, WA) depending on patient proximity to the device within the department. Investigators measured vessels in short-axis

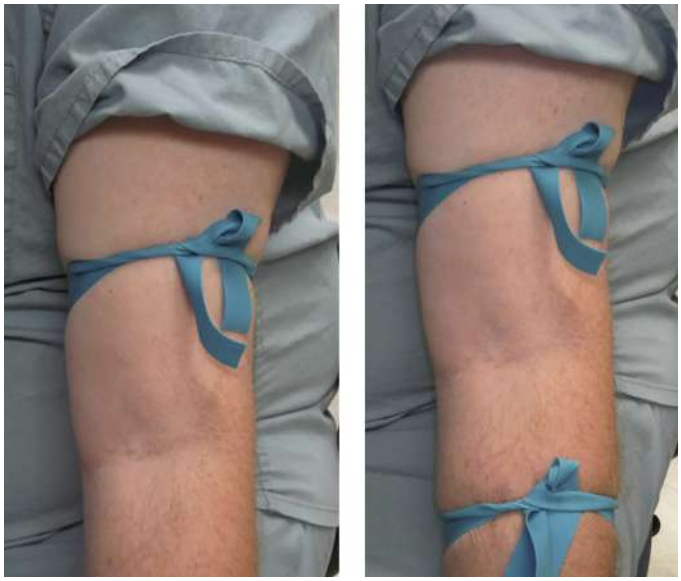

Figure 1. Standard tourniquet pictured left; double tourniquet pictured right.

orientation and assessed diameter pre- and post- tourniquet. The US site director reviewed all scans and measurements for accuracy. There were no discrepancies in measurements of vein depth between the initial operators and the director's review. A 4.78 cm 20-gauge, peripheral IV catheter was used for the evaluation. Investigators recorded first-stick success, number of attempts, and overall success of the procedure as well as the location of insertion (upper arm, antecubital, forearm) of all successful placements. A successful insertion was confirmed by full advancement of the catheter so that the catheter was no longer externally visible, immediate sampling of at least five cubic centimeters (cc) of blood, and flushing without resistance of five cc of saline.

Patient, IV, and vein characteristics at time of initial assessment were summarized for each study group using medians and interquartile ranges for continuous variables and compared by Kruskal-Wallis tests. We summarized frequencies and percentages for categorical variables and compared them by chi-squared tests or Fisher's exact tests. Logistic regression was employed to assess the strength of association between type of IV inserters and first-stick success. All tests of statistical significance were two-sided with a p-value < 0.05 indicating a significant difference. We performed analyses using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Additional data collected from the electronic health record included age, gender, body mass index (BMI), vitals signs, and relevant past medical history.

The primary outcome was the first-stick success rate of obtaining venous access between the two groups. This was assessed by the number of attempts to establish access. We performed statistical comparisons using chi-squared and Fisher's exact tests. All tests of statistical significance were two-sided with a p-value <0.05 indicating significant difference.

RESULTS

We consented and enrolled 100 patients in the study. Data from 99 patients was available for the final analysis. One patient was excluded due to prior enrollment discovered after randomization (Figure 2). Table 1 illustrates patient demographics with no statistical difference between groups regarding age, gender, BMI, and vital signs.

Veins were deeper in the DT group compared with the ST group at 0.73 cm vs 0.87 cm, respectively (p=0.02). After tourniquet application, veins dilated in both ST and DT groups. However, there was no significant difference in the amount of change in vein diameter between ST and DT groups. Vein characteristics prior to insertion are shown in Table 2.

First-stick success was similar in both groups with successful insertion in 38, or 79.2%, in the ST group vs 39, or 76.5%, in the DT group (p = 0.75). Overall success was similar in both groups with only one failure in each group resulting in 47 (97.9%) and 50 (98.0%) success in ST and DT groups respectively (p = 0.96). The two groups underwent similar rates of blind attempts prior to study enrollment with an average of 2.0 in each group (p = 0.82), and both groups yielded successful IV placement after an average of one attempt (p = 0.88). One failure in the DT group underwent five attempts at placement before opting out of further participation in the study.

Attending physicians and non-attending providers inserted catheters for this evaluation. Attendings inserted 20 in the ST group and 19 in the DT group, totaling 42% and 41% of total catheters inserted in each group respectively. Attending physicians were overall more successful with first attempt in 20 (100%) of ST cases and 19 (90.5%) of DT cases (p=0.49) compared to non-attendings' first-stick success of 18 (64.3%) and 20 (66.7%) for ST and DT groups (0.85), respectively. Table 3 shows breakdown of first-stick success by type of inserter. Table 3 also shows significantly higher percentages of first-stick success of ST and DT placement by attending physicians (95%) compared to non-attending inserters (65%). Attending physicians are 10 times more likely to have first-stick successful IV placement in contrast to non-attendings (odds ratio: 10.3, 95% confidence interval, 2.2 to 46.9).

Further investigation regarding location of IV placement did demonstrate a lower success rate in the upper arm when compared to the antecubital and forearm; however, this difference did not approach clinical significance. This overall trend bore out when divided into ST and DT technique. Table 4 demonstrates vein location in the arm.

DISCUSSION

Vein dilation devices have a role in USGPIV insertion as a larger venous target may facilitate IV insertion. The Esmarch bandage, Rhys-Davis exsanguinator, and a vacuum device have all been described as routes to augment vein size, in addition to

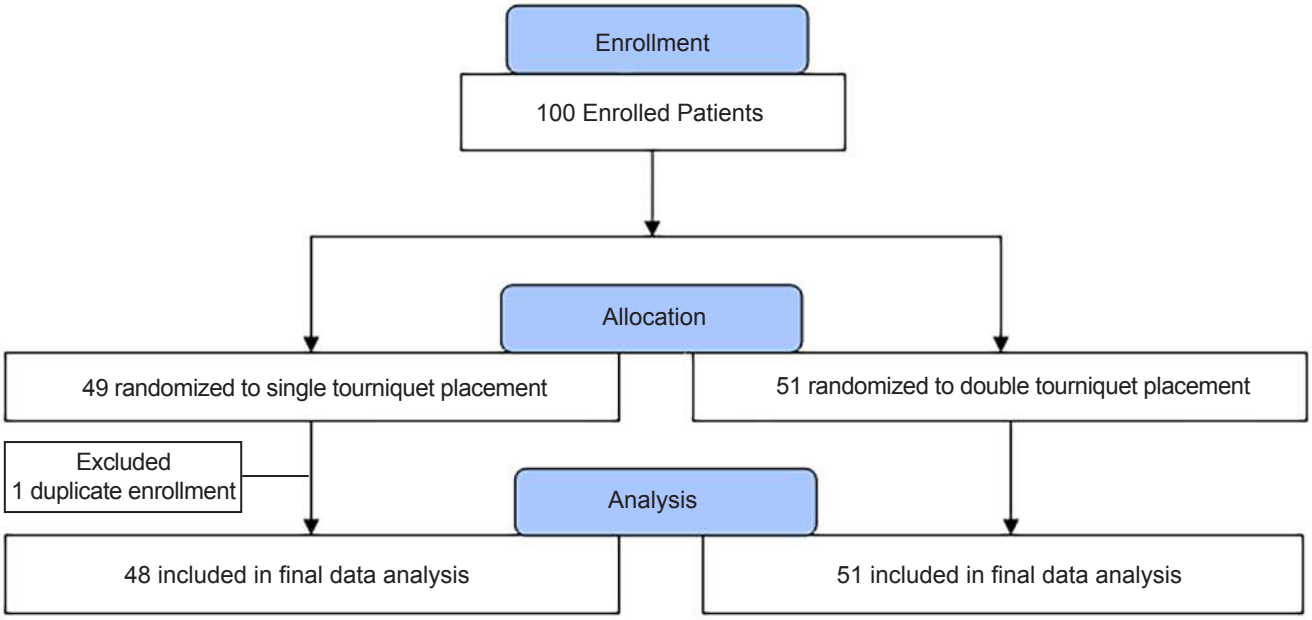

Figure 2. Enrollment Flowchart.

the local application of nitroglycerine ointment.[13-15] Tourniquets and blood pressure cuffs that may be applied for vein enhancement are readily available and ubiquitous in most EDs and inpatient wards. While blood pressure cuffs are pressure controlled and tightness around the arm can be uniformly standardized using this device, the blood pressure cuff also occupies a large portion of the arm, limiting location of sites for IV insertion to the antecubital fossa and forearm. Therefore, we chose to evaluate strategic application of a practical solution, namely tourniquets, for this intervention.

We used first-stick success as the primary outcome in our study as it is one of the quality and safety goals of our vascular access program. Past studies of difficult peripheral IV access have demonstrated that patients requiring multiple attempts or physician intervention could have a delay of access of up to two hours,[16] which in turn can lead to a delay of both care and treatment. Repeated access attempts also correspond to more time spent by technician, nursing, and physician staff members away from other tasks. As equipment preparation has been identified as an area of increased risk for needlestick injuries,[17] attempts beyond the first may represent a hazard to the inserter as well.

Unquestionably, multiple punctures by a needle and increased tourniquet time are uncomfortable for patients from both a physical and at times psychological perspective.[18] Additionally, repeated venipuncture performed prior to successful line placement may result in increased vessel wall damage, which in turn raises concern for development of phlebitis and even the potential for thrombus formation. Ultrasound IVs have also been identified with increased risk of extravasation upon administration of contrast for computed tomography.[19] Damage to the endothelium from multiple attempts may raise this risk as well.

Attending faculty experienced a very high first-stick success with 100% in the ST cohort and 90.5% in the DT cohort. As inserters become more experienced with the procedure, the potential benefit of adding a tourniquet also diminishes and would require a very large sample size to demonstrate whether a statistical difference truly existed. Resident, nurse, and technician inserters had very similar rates of success between arms, 64.3% in ST vs 66.7% in DT, and while a larger study may reveal an actual difference in success rates, our results do not suggest significant benefit to an added tourniquet.

While location of the vessel did not favor one location to the point of clinical significance, a trend toward increased success in the forearm and antecubital location was noted. While past studies have focused more upon longevity than ease of cannulation in comparison of access sites,[20] further investigation to compare the success rates between locations may be warranted. If the upper arm truly is more difficult to access upon initial puncture in addition to having less robust longevity, pursuing it as a site of access may be more appropriate as a back-up choice.

LIMITATIONS

There were several limitations to our investigation. We did not account for compressibility of the vein in this trial, the key difference observed between double and single tourniquet in previous comparisons of the techniques.[12] Although we measured vein dilation in both groups, it is possible that compressibility

Table 1. Patient Characteristics.[§]

	ST (n=48)	DT (n=51)	p-value
Age	58 (43, 75)	62 (43, 75)	0.64
Female (%)	34 (72.3%)	42 (82.3%)	0.23
History difficult access (%)	31 (64.6%)	32 (62.7%)	0.85
IV drug use (%)	3 (6.2%)	3 (5.9%)	1.00
Hemodialysis (%)	10 (20.8%)	7 (13.7%)	0.35
Obese (%)	24 (50.0%)	25 (58.9%)	0.49
Body Mass Index	30.1 (25.8, 36.0)	30.2 (25.1, 37.1)	0.72
Vital signs			
Systolic BP	137.5 (117.0, 154.0)	131.0 (118.0, 151.0)	0.73
Diastolic BP	71.5 (58.0, 89.0)	74.0 (58.0, 89.0)	0.94
HR	88.5 (74.5, 108.0)	90.0 (78.0, 101.0)	0.84
RR	18.0 (18.0, 20.0)	18.0 (18.0, 22.0)	0.24
Temperature, °C	36.9 (36.6, 37.0)	36.8 (36.6, 37.0)	0.90

ST, single tourniquet; *DT,* double tourniquet; *BP*, blood pressure; *HR,* heart rate; *RR*, respiratory rate.
[§] For continuous variables, medians (interquartile ranges) were presented. For categorical variables, frequencies (percentages) were presented.

Table 2. Vein Characteristics.[§]

	ST (n=48)	DT (n=51)	p-value
Depth of vein, cm	0.73 (0.61, 0.94)	0.87 (0.71, 1.27)	0.02
Pre-diameter of vein, cm	0.25 (0.20, 0.32)	0.24 (0.20, 0.32)	0.86
Post-diameter of vein, cm	0.29 (0.23, 0.37)	0.29 (0.22, 0.37)	0.73
Change of vein diameter, cm	0.04 (0.01, 0.06)	0.03 (0.01, 0.08)	0.59

ST, single tourniquet; *DT*, double tourniquet; *cm*, centimeter.
[§]For continuous variables, medians (interquartile ranges) were presented. For categorical variables, frequencies (percentages) were presented. There were 9 to 12 missing observations on depth of vein and diameter of vein in each group.

may impact successful cannulation independent of vein size. As standard tourniquets do not have pressure control capability, differences in vein dilation and compressibility may partly be due to the degree of tightness with which the tourniquet was applied.

In a previous comparison of ST vs DT, tourniquet placement was standardized and specific vessels in the arm were measured.[12] In our study, the selection of vessel and subsequent tourniquet placement was left to the discretion of the inserters in anticipation of variation of vein depth and accessibility across our patient population. We also believe this more realistically reflects the clinical process of establishing US-guided IV access with variation in inserter preference or comfort regarding vessel selection. Standardization of device placement and vein in question may have demonstrated a more consistent effect within each and between the two groups as well as providing a more consistent vein depth across the study.

There was a statistically significant difference in depth of vein between groups, and this may have impacted first-stick success rates. Vein depth is related to success of US-guided IV cannulation. Although the literature supports a depth of 1.20 cm as being a distance with increased failures of insertion,[20] moving from 0.73 cm to 0.87 cm can create more difficulty with insertion and threading of the catheter. Deeper vessels can also run into challenges with seating a sufficient length of catheter in the vessel. A decreased percentage of the catheter residing in the vessel has been strongly associated with a higher hazard of failure,[21] although this appears to reflect more directly on the catheter's longevity rather than the ease of placement. However, a deeper vein may also require insertion at a steeper angle to achieve a greater length in the vessel, and steeper angles in turn can create challenges with successfully advancing a catheter without vessel injury or backwalling.

Finally, we performed no power analysis in our study. Our goal was simply to recruit a convenience sample of subjects over

Table 3. IV Characteristics at time of initial assessment.[§]

	ST	DT	p-value
n	48	51	
IV placed by (%)			
Attending physicians	20 (41.7%)	21 (41.2%)	0.96
Non-attending inserters	28 (58.3%)	30 (58.8%)	
IV location in arm (%)			
Antecubital	21 (44.7%)	30 (60.0%)	0.27
Forearm	14 (29.8 %)	9 (18.0%)	
Upper	12 (25.5%)	11 (22.0%)	
First-stick success (%)			
Yes	38 (79.2%)	39 (76.5%)	0.75
No	10 (20.8%)	12 (23.5%)	
Overall success (%)			
Yes	47 (97.9%)	50 (98.0%)	0.96
No	1 (2.1%)	1 (2.0%)	
Number of blind attempts	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	
Number of attempts	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	
IV placed by attending physicians (n=41)			
n	20	21	
First-stick success (%)			
Yes	20 (100.0%)	19 (90.5%)	0.49
No	0 (0.0%)	2 (9.5%)	
IV placed by non-attending inserters (n=58)			
n	28	30	
First-stick success (%)			
Yes	18 (64.3%)	20 (66.7%)	0.85
No	10 (35.7%)	10 (33.3%)	

ST, single tourniquet; *DT*, double tourniquet.
[§]For continuous variables, medians (interquartile ranges) were presented. For categorical variables, frequencies (percentages) were presented. There was a missing observation on IV location in each group.

a limited amount of time; therefore, we did not conduct a sample size calculation or power analysis. Due to the lack of published data on this particular technique, key assumptions required for a calculation of sample size were not available. Nonetheless, our study may have been underpowered to reveal a significant difference in success between the two techniques.

CONCLUSION

Single tourniquet vs double tourniquet technique does not impact first-stick success of the provider inserting the IV, regardless of his or her level of experience. Further investigations comparing these techniques under standardized technique and depth are needed to fully assess whether an added tourniquet provides any added success in first-stick success.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

Table 4. Results of intravenous placement by type of location in arm.[§]

	Single tourniquet		p-value
IV location in arm (%)	Success (n=38)	Failure (n=9)	
Antecubital	18 (85.7%)	3 (14.3%)	0.41
Forearm	12 (85.7%)	2 (14.3%)	
Upper	8 (66.7%)	4 (33.3%)	
	Double tourniquet		p-value
IV location in arm (%)	Success (n=39)	Failure (n=11)	
Antecubital	24 (80.0%)	6 (20.0%)	0.40
Forearm	8 (88.9%)	1 (11.1%)	
Upper	7 (63.6%)	4 (36.4%)	
	All (single/double tourniquet)		p-value
IV location in arm (%)	Success (n=77)	Failure (n=20)	
Antecubital	42 (82.3%)	9 (17.7%)	0.14
Forearm	20 (87.0%)	3 (13.0%)	
Upper	15 (65.2%)	8 (34.8%)	

[§]There was a missing observation on IV location in each group.

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How Well Does the Standardized Video Interview Score Correlate with Traditional Interview Performance?

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Section Editor: Jeffrey Druck, MD
Submission history: Submitted February 12, 2019; Revision received June 20, 2019; Accepted July 10, 2019
Electronically published August 20, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.42731

Introduction: In 2017, all medical students applying for residency in emergency medicine (EM) were required to participate in the Standardized Video Interview (SVI). The SVI is a video-recorded, unidirectional interview consisting of six questions designed to assess interpersonal and communication skills and professionalism. It is unclear whether this simulated interview is an accurate representation of an applicant's competencies that are often evaluated during the in-person interview.
Objective: The goal of this study was to determine whether the SVI score correlates with a traditional in-person interview score.

Methods: Six geographically and demographically diverse EM residency programs accredited by the Accreditation Council for Graduate Medical Education participated in this prospective observational study. Common demographic data for each applicant were obtained through an Electronic Residency Application Service export function prior to the start of any scheduled traditional interviews (TI). On each TI day, one interviewer blinded to all applicant data, including SVI score, rated the applicant on a five-point scale. A convenience sample of applicants was enrolled based on random assignment to the blinded interviewer. We studied the correlation between SVI score and TI score.

Results: We included 321 unique applicants in the final analysis. Linear regression analysis of the SVI score against the TI score demonstrated a small positive linear correlation with an r coefficient of +0.13 (p=0.02). This correlation remained across all SVI score subgroups (p = 0.03).

Conclusion: Our study suggests that there is a small positive linear correlation between the SVI score and performance during the TI. [West J Emerg Med. 2019;20(5)726-730.]

INTRODUCTION

The screening, interviewing, and ranking processes for residency programs are critical and have enduring consequences for the overall program. Residency leadership is tasked with identifying applicants who are a "good fit" for the program and have both a high likelihood of success and low likelihood of poor performance. This can be challenging when faced with applications that number in the hundreds to thousands in a typical application cycle. Traditional interviews (TI) are designed to assess for noncognitive factors, such as interpersonal and communication skills, maturity, interest in the field, dependability, and honesty, which cannot be easily assessed through other means.[1]

In 2017, the Association of American Medical Colleges (AAMC) required all medical students applying for residency in emergency medicine (EM) to complete the Standardized Video Interview (SVI) as part of the application process. The ultimate goal is to extend this to other specialties as well. The SVI is a recorded, asynchronous, and uni-directional video interview that consists of six questions presented in text prompts. Students have 30 seconds to read each question and up to three minutes to record a response. Each response is rated on a five-point scale that ranges from 1 = rudimentary to 5 = exemplary and the total score is calculated as the sum of the ratings from each response for a total score range of 6-30.[2] Residency programs may view each applicant's total score and also the entire video response of all six questions.

The SVI is designed to assess (1) interpersonal and communication skills, and (2) knowledge of professional behaviors.[2] Previously, these two competencies could only be indirectly measured through personal statements, standardized letters of evaluation (SLOE), and selected quotes from each applicant's medical student performance evaluation.[3-5] Although the AAMC explicitly states that the SVI "is not intended to replace in-person interviews,"[2] we sought to determine whether there is any correlation between the SVI and the TI. Given the large volume of applicants to each residency program, it is possible that some programs may use the SVI as a proxy measure of an applicant's competencies that are often evaluated during the in-person interview. However, it is unclear if this simulated interview format is an accurate representation of an applicant's relevant competencies. The goal of this study was to determine how well (if at all) the SVI score correlates with an in-person TI.

Population Health Research Capsule

What do we already know about this issue?
The Standardized Video Interview (SVI) is a uni-directional video interview with six questions that assess interpersonal and communication skills and professionalism.

What was the research question?
Our goal was to determine whether the SVI score correlates with a traditional in-person interview (TI) score.

What was the major finding of the study?
The SVI score demonstrated a small, positive linear correlation with the TI score that remained across all SVI score subgroups.

How does this improve population health?
While the SVI may provide an estimate of an applicant's performance on a TI, it may not be a true replacement for a traditional interview.

METHODS

This was a prospective, observational, multicenter study conducted from October 2017–February 2018. Six EM residency programs accredited by the Accreditation Council for Graduate Medical Education (ACGME) participated in the study. Common demographic data for each applicant (gender, age, and United States Medical Licensing Exam score) were obtained through an Electronic Residency Application Service (ERAS) export function prior to the start of any scheduled TIs. During each TI day, one interviewer at each site was blinded to all applicant data, including the SVI score. This blinded interviewer met the applicant with no previous information regarding that applicant. The blinded interviewer was then asked to rate the TI on a five-point Likert scale (1 = rudimentary; 2 = below average; 3 = average; 4 = above average; 5 = exemplary) that was developed a priori through consensus by the authors. The scale was deemed to have face validity based on review by multiple residency program directors involved in this study. The blinded interviewer based his or her TI score purely on the interview. When a single applicant was interviewed at more than one program participating in this study, the mean TI score was used.

A convenience sample of applicants was enrolled based on random assignment to the blinded interviewer. Inclusion criteria were applicants assigned to the blinded interviewer at a participating site. Exclusion criteria included prior knowledge of the applicant by the interviewer and no SVI score available for the applicant. We studied the correlation between SVI score and TI score. Predetermined subgroup analysis was performed based on applicants' SVI scores as follows: 6-11, 12-17, 18-23, 24-30. These SVI score ranges are described by the AAMC as representing different proficiency levels on the target competencies.[6]

We used linear regression analysis to assess the relationship between SVI score and TI score. Analysis of variance (ANOVA)

was used to determine the variation of mean TI score with the SVI subgroup score. Interrater reliability of TI for applicants who interviewed at more than one program was calculated using the intraclass coefficient.

This study was reviewed by the institutional review board at the primary site.

RESULTS

Six ACGME-accredited EM residency programs participated in the study. Demographic data are listed in Table 1. A total of 344 applicants were assigned to a blinded interviewer. Seven were excluded due to prior knowledge of the applicant, and 16 were excluded as no SVI had been completed. This left 321 unique applicants for final analysis. Demographic data were available for 318 (Table 2) as some institutions blocked ERAS demographics.

SVI scores for the applicants ranged from 10-28 (mean = 20 ± 2.8). Interview scores ranged from 1-5 (mean = 3.4 ± 0.9). Linear regression analysis of the SVI score against the TI score demonstrated a small, positive linear correlation with an *r* coefficient of +0.13 (p = 0.02). When separating SVI scores into subgroups, this relationship between the SVI score and the TI score remained (p = 0.03) (Table 3).

Thirty-four applicants had interviews at more than one site (range 2-3 sites, mean 2.1). The intraclass coefficient of TI scores for these applicants was low (ICC = 0.023).

DISCUSSION

Residency programs receive hundreds to thousands of medical student applications each year. Screening this volume of applications to decide which applicants to invite to interview can be daunting, and much of the process remains subjective. There have been many attempts at innovative approaches to standardization of the application process over the past several years. Most notably, this includes the SLOE, which is widely used by EM clerkship directors to provide grading transparency and standardization.[7] Similarly, the AAMC has now developed the SVI as another tool for residency programs to help differentiate students in the competencies of interpersonal and communication skills and professionalism in a more standardized fashion prior to TI.

We found, not surprisingly, that there was a small, positive linear correlation between the SVI score and the TI score. This correlation remained across all SVI score subgroups. As the SVI score increased, the TI score increased as well. This suggests that, in many cases, the SVI may provide an estimate of an applicant's performance on a TI. SVI and TI may be assessing the same qualities in applicants, such as verbal communication skills, emotional intelligence, teamwork and leadership, empathy and altruism, ethics, cultural competence, and conscientiousness.[1,2] Although we found a positive correlation between the SVI and the TI, the *r* coefficient was low (*r* = +0.13). For every one point increase in SVI score, the TI increased by 0.04. This indicates

Table 1. Demographic data of residency programs and traditional interviewers.

Residency programs		
Number of programs	6	
University	5 (83%)	
Community	1 (17%)	
Northeast	3 (50%)	
South	2 (33%)	
West	1 (17%)	
Interviewers		**Years of experience interviewing applicants (Range; Mean ± SD)**
Number of interviewers	50	1-25; 5.8 ± 6.1
Position		
Chair	1 (2%)	8
Program Director	1 (2%)	15
Associate/Assistant Program Director	5 (10%)	3-20; 7.6 ± 7.1
Clerkship Director	1 (2%)	10
Core Faculty	10 (20%)	4-25; 12 ± 7.3
General Faculty	21 (42%)	1-20; 4 ± 4.2
Chief Resident	4 (8%)	1
Resident	7 (14%)	1-3; 1.9 ± 0.7

SD, standard deviation.

Table 2. Demographic data of residency applicants.

Demographic	N=318	Range	Median	Mean
Age		23-38	27	27.1 ± 2.4
Gender (n=312)				
Male	192 (61.5%)			
Female	120 (38.5%)			
Medical School				
Northeast	131 (41.2%)			
Central	50 (15.7%)			
South	92 (28.9%)			
West	33 (10.4%)			
International	12 (3.8%)			
US Private	122 (38.4%)			
US Public	158 (49.7%)			
Osteopathic	26 (8.2%)			
International	12 (3.8%)			
USMLE Step 1		195-272	235	235.5 ± 15.1
USMLE Step 2 CK		215-284	250	248.8 ± 13.5
USMLE Step 2 CS				
Pass	100%			
COMLEX Level 1		430-773	598	591.3 ± 85.5
COMLEX Level 2 CE		501-913	617	634.9 ± 110
COMLEX Level 2 PE				
Pass	100%			

USMLE, United States Medical Licensing Exam; *CK,* clinical knowledge; *CS,* clinical skills; *COMLEX,* Comprehensive Osteopathic Medical Licensing Exam; *CE,* cognitive evaluation; *PE,* performance evaluation.

that while the SVI may approximate the TI, it may not be a true replacement for a real interview.

While we have demonstrated through our analysis that the SVI may be a proxy for an interviewer assessing an applicant in a TI, it does not provide the applicant an opportunity to learn more about the residency program and determine their "fit."[8,9] In addition, many interview days are preceded by a pre-interview social event during which the applicants may freely interact with the residents without the formal constraints of the interview day.[10] The uni-directional SVI format does not allow for this bi-directional matching process between the applicants and programs and for this reason is unlikely to ever fully replace the TI day.

LIMITATIONS

Although this was a multicenter study that included a diverse representation of residency programs, only 321 of the 2901 applicants to EM residency programs during this application cycle were included for analysis. This may limit the overall generalizability of our findings. In addition, we did not use structured interviews. Each blinded traditional interviewer was allowed to ask the questions that he or she typically asks and conduct themselves during the interview process as they normally would, independent of the study. We felt that this would be more reflective of the real-world performance of the TI. However, not surprisingly, we found a low interrater reliability (intraclass correlation coefficient = 0.023) among a high number of interviewers (n = 50). This is an interesting result in and of itself, irregardless of the SVI. This may reflect a varied interview process at each of the different participating sites, making it difficult to compare TI scores from program to program. Lastly, we only included applicants who were randomly assigned to a blinded interviewer, which may have resulted in a sample bias.

CONCLUSION

Our study suggests that there is a small, positive linear correlation between the Standard Video Interview and performance during the traditional interview. Future directions include determining which aspects of interview performance are assessable by both the SVI and the TI and which are uniquely measured by the TI alone.

Table 3. Relationship between the Standardized Video Interview score and traditional interview score by subgroup.

SVI Score Subgroup	N	Mean TI Score	P
6-11	1	3	
12-17	55	3.1 ± 0.9	0.03*
18-23	225	3.46 ± 0.9	
24-30	40	3.51 ± 0.9	

SVI, Standardized Video Interview; *TI,* traditional interview.
* p<0.05 denotes statistical significance.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Evaluating a Novel Simulation Course for Prehospital Provider Resuscitation Training in Botswana

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Section Editor: Chadd K. Kraus, DO, DrPH, MPH
Submission history: Submitted November 15, 2018; Revision received June 6, 2019; Accepted June 11, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.6.41639

Introduction: In 2012, Botswana embarked on an organized public approach to prehospital medicine. One goal of the Ministry of Health (MOH) was to improve provider education regarding patient stabilization and resuscitation. Simulation-based instruction is an effective educational strategy particularly for high-risk, low-frequency events. In collaboration with partners in the United States, the team created a short, simulation-based course to teach and update prehospital providers on common field responses in this resource-limited setting. The objective of this study was to evaluate an educational program for Botswanan prehospital providers via written and simulation-based examinations.

Methods: We developed a two-day course based on a formal needs assessment and MOH leadership input. The subject matter of the simulation scenarios represented common calls to the prehospital system in Botswana. Didactic lectures and facilitated skills training were conducted by U.S. practitioners who also served as instructors for a rapid-cycle, deliberate practice simulation education model and simulation-based testing scenarios. Three courses, held in three cities in Botswana, were offered to off-duty MOH prehospital providers, and the participants were evaluated using written multiple-choice tests, videotaped traditional simulation scenarios, and self-efficacy surveys.

Results: Collectively, 31 prehospital providers participated in the three courses. The mean scores on the written pretest were 67% (standard deviation [SD], 10) and 85% (SD, 7) on the post-test ($p < 0.001$). The mean scores for the simulation were 42% (SD, 14.2) on the pretest and 75% (SD, 11.3) on the post-test ($p < 0.001$). Moreover, the intraclass correlation coefficient scores between reviewers were highly correlated at 0.64 for single measures and 0.78 for average measures ($p < 0.001$ for both). Twenty-one participants (68%) considered the course "extremely useful."

Conclusion: Botswanan prehospital providers who participated in this course significantly improved in both written and simulation-based performance testing. General feedback from the participants indicated that the simulation scenarios were the most useful and enjoyable aspects of the course. These results suggest that this curriculum can be a useful educational tool for teaching and reinforcing prehospital care concepts in Botswana and may be adapted for use in other resource-limited settings. [West J Emerg Med. 2019;20(5)731-739.]

INTRODUCTION

Organized prehospital services in lower- and middle-income countries (LMIC) in sub-Saharan Africa continue to be in earlier stages of development compared to other regions worldwide. Only a minority of Africans (<9%) are covered by an emergency medical services (EMS) system.[1] Implementation and development of an EMS system has had varied outcomes among LMICs. In 2012 the Ministry of Health (MOH) of Botswana established the country's first public, prehospital EMS program.

At its inception, the Botswana public EMS program recruited most staff from MOH healthcare providers who were previously employed as nurses and healthcare attendants even though they did not have prior experience in prehospital care. A physician is the medical director of the public EMS system; however, physicians are not involved in the day-to-day work of the system. At the time of this study, the sole paramedic (trained internationally) in the EMS system served as its head of operations. Specific training, accreditation, and licensure requirements are necessary for a person to be identified as an emergency medical technician (EMT), either "basic" or "advanced."

Boitekanelo College, a college that focuses on healthcare education in Gabarone, first started offering certificate diplomas and degree programs in EMS in 2011. However, few employees of the public EMS system were graduates of these programs at the time of this study, and there was no mandatory prehospital training for those newly employed by the system. At the time of this study, 115 EMS staff in Botswana (nurses, EMTs, healthcare assistants, and drivers) were stationed at six different EMS centers. As with many existing programs in sub-Saharan Africa, the Botswana EMS system offers primarily (but not always) basic life services, is financed and operated by the government, and has a public access telephone number for first response.

Poor outcomes in developing EMS systems are often due to a lack of resources, insufficient training, and other system deficiencies.[2] The Botswana MOH has focused on optimizing the education and training of workers for initial patient stabilization and resuscitation. We created a curriculum designed to augment the training of prehospital care providers and enhance provider performance and patient outcomes. A critical step toward advancing prehospital care training in Botswana was to identify, establish, and promote sustainable instruments that were specifically suited to serve the local emergency medical conditions.[3] Hence, we used the results of a formal needs assessment[4] to better tailor an educational initiative.

The needs assessment of the Botswana MOH and Gaborone EMS system helped us to identify knowledge gaps and opportunities for educational development. Administrators and providers felt that prehospital providers were not optimizing opportunities for resuscitative interventions either in the field or en route to the hospital, partly because they were not familiar with supplies, lacked confidence in intervening, and failed to identify opportunities for intervention. The leading causes of EMS transport in the survey corresponded with the leading causes of EMS transport in Africa, namely, injury, obstetric, respiratory, cardiovascular, and gastrointestinal complaints.[1] We found that medical simulation could be useful in addressing the needs of prehospital providers.

Simulation-based medical education enables providers to reproducibly practice high-risk scenarios in a safe learning environment. Simulation helps advance clinical knowledge, procedural skills, confidence, teamwork, and effective communication practices. The efficacy of this training tool for prehospital medicine has been established previously.[5] Specifically, the rapid-cycle deliberate practice (RCDP) format was chosen for this particular population because it is well suited to those with less exposure to learning via the use of medical simulation and for those with the goal of attaining mastery.[6] RCDP is an instructional method of simulation-based learning that combines multiple, shorter repetitions of cases with intermixed feedback and has been shown to improve key performance measures in resuscitation,[6,7] specifically in teaching concepts of resuscitation in cardiac arrest, including assisted respiration, compressions, and defibrillation.[8,9]

We developed, implemented, and evaluated a simulation-based resuscitation curriculum for prehospital providers in Botswana. Outcomes included provider satisfaction with the curriculum and improvement of knowledge based on pre- and post-testing.

Population Health Research Capsule

What do we already know about this issue?
Prehospital medical systems in low- and middle-income (LMIC) countries are actively being developed. Medical simulation has been shown to be an effective teaching tool.

What was the research question?
We examined whether a novel, simulation-based course would be an effective teaching tool for prehospital providers in Botswana.

What was the major finding of the study?
Over half of public Botswanan prehospital providers enrolled. Their test scores improved, and the course was well received.

How does this improve population health?
We hope to teach this course regularly in Botswana and believe it can be adapted for use in other LMICs to help improve the effectiveness of prehospital care.

METHODS

We developed a two-day, simulation-based training curriculum based on a formal needs assessment along with input from the Botswana MOH leadership. Simulation scenarios were based on the most frequent calls to the prehospital system, including abdominal pain, trauma, obstetric/gynecologic complications, respiratory distress, and weakness. The medical faculty from the U.S. presented supplementary didactic talks on how to approach medical simulation and a brief overview of approaching prehospital trauma specifically by request of the EMS administration. In addition, they conducted procedural-skills training sessions on intravenous/intraosseous access and oxygen delivery and instructed on RCDP simulation-based testing scenarios. The course was held in each of the three largest Botswanan cities: Gaborone, Francistown, and Mahalapye; it was offered to off-duty prehospital providers employed by the MOH. The participants were evaluated with written, multiple-choice tests, videotaped traditional simulation scenarios, and self-efficacy surveys administered before and after the training.

This study received institutional review board permission from the associated institutions both in the U.S. and the Botswana MOH.

Study Population and Eligibility Criteria

Prehospital EMTs and nurses who were not on active duty during the training period were eligible to participate in the course (Table 1). The head of EMS requested that healthcare attendants and drivers should not participate in this training. In total, 31 (67.4%) of 46 prehospital providers in Botswana met the eligibility criteria and were included in the study. Due to the limited number of prehospital providers in the country, we decided not to have a comparison group for this study. However, to achieve the largest possible enrollment of off-duty providers, we offered the course three times in the three largest cities in Botswana.

Table 1. Total staffing within Botswana's public emergency medical services system.

City	Emergency medical technicians	Registered nurses	Total
Francistown*	4	9	13
Gaborone*	5	8	13
Selebi-Phikwe	0	6	6
Mahalapye*	3	2	5
Palapye	0	5	5
Lobaste	0	4	4
Total	12	34	46

*Location of training.

Data Management

We selected pairwise deletion as the most appropriate approach to address missing data. Specifically, for each analysis we included all observations with non-missing values for all variables relevant to that analysis. To enable quantitative analysis of self-efficacy survey data, Likert items were scored ranging from 1 for "extremely uncomfortable" to 7 for "extremely comfortable."

Statistical Analysis

Descriptive Statistics

Frequencies and percentages (for categorical variables) or medians and interquartile ranges (IQR) (for continuous variables) associated with demographic characteristics were calculated and reported.

Pre- vs Post-training Comparison

We compared continuous variables (written and simulation test scores) between two dependent groups (pre- and post-training) using the paired *t*-test, while ordinal variables (participant-reported, self-efficacy scores) were compared between two dependent groups (pre- and post-training) using the Wilcoxon signed-rank test.

Interclass Correlation

We used the Pearson correlation coefficient to determine interclass correlation between reviewers' assessments of the simulation-based tests and associations between all three testing modalities (self-efficacy survey and written and simulation-based tests).

Assumptions and Tools

Hypothesis testing was considered statistically significant at $p < 0.05$. We performed all statistical analyses in Stata Statistical Software 15.1 (StataCorp 2017, College Station, TX, USA). Tables were computed using Microsoft Excel 2016 (Microsoft, Redmond, WA, USA).

RESULTS

Demographic Characteristics

Table 2 describes the participants' demographic characteristics. Overall, 31 prehospital providers (19 [61%] male, 12 [39%] female) met the eligibility criteria and were included in the study. The participants were distributed roughly equally among the three study sites, including Francistown (10/31, 32.3%), Mahalapye (10/31, 32.3%), and Gaborone (11/31, 35.4%). The median number of years working in healthcare and in EMS was 6.0 years (IQR = 3.0–8.0) and 2.0 years (IQR = 1.0–2.0), respectively. The median number of self-reported, adult resuscitations performed in the past year was 1.0 (0–10 resuscitations). Prior to working in EMS, the participants had received training in Basic Life Support (20/31, 65%), Intermediate Life Support (10/31, 32%), Advanced Cardiovascular Life Support (3/31, 10%), and either Advanced

Table 2. Characteristics of study participants in a course designed to improve prehospital care.

Characteristics	Frequency (%) N = 31
Sex	
Male	19 (61%)
Female	12 (39%)
Study site	
Francistown	10 (32%)
Gaborone	11 (35%)
Mahalapye	10 (32%)
Years in health care, median (IQR)	6.0 (3.0, 8.0)
Years in EMS, median (IQR)	2.0 (1.0, 2.0)
Adult resuscitations in the past year, median (IQR)	1.0 (1.0, 2.0)
Basic life support training	
No	11 (35%)
Yes	20 (65%)
Intermediate life support training	
No	21 (68%)
Yes	10 (32%)
Advanced cardiovascular life support training	
No	28 (90%)
Yes	3 (10%)
Advanced or international trauma life support training	
No	21 (68%)
Yes	10 (32%)

IQR, interquartile range; *EMS,* emergency medical services.

Trauma Life Support or International Trauma Life Support (10/31, 32%). All certifications were reported based on published international and U.S. standards, as suggested.

What is the impact of the curriculum on the self-reported self-efficacy of prehospital providers?

To determine the curriculum's impact on the participants' confidence in evaluating and managing adults with emergency conditions, we required that they complete a 14-item, self-efficacy survey before and after the training was implemented (Appendix A). The survey items were rated on a Likert scale from 1 (extremely uncomfortable) to 7 (extremely comfortable). Baseline self-efficacy scores are summarized in Table 3, and Table 4 compares the post-test scores.

What is the impact of the curriculum on prehospital providers' performance as measured by the written and simulation-based tests?

To evaluate the impact of the training curriculum on the participants' knowledge and performance in evaluating and managing adults with emergency conditions, we required that they complete both the written (Appendix B) and simulation-based (Appendix C) tests before and after the training was implemented. The participants' performance on each test was reported as a percentage. Table 5 and Figure 1 show the participants' mean scores on both tests, before and after the training. Two reviewers independently rated each participant on the simulation test. The Pearson correlation coefficient was calculated to measure the interclass correlation between the two reviewers (Table 6).

What is the association between participants' written test scores, participant-reported self-efficacy, and performance on the simulation-based test?

To validate the written test score, we compared the participants' scores on the written test to their self-efficacy scores and their simulation-based test scores using the Pearson correlation coefficient (Table 7). The pre-training written test scores and the pre-training simulation test scores had a moderate positive correlation ($r = 0.41$, $p = 0.04$). No significant correlation was observed between the corresponding post-training scores. Although the pre-training written score was positively correlated with the pre-training self-efficacy score, this finding was not statistically significant ($r = 0.34$, $p = 0.06$). In addition, we observed no significant correlation between the post-training written test and self-efficacy scores.

Table 3. Participants' reported self-efficacy for various emergency medical services activities post-training.

Item	Rank	Pre-test frequency	Post-test frequency
Administering oxygen	Slightly comfortable	2 (6%)	
	Very comfortable	12 (39%)	6 (19%)
	Extremely comfortable	17 (55%)	25 (81%)
Placing an airway adjunct	Extremely uncomfortable	2 (6%)	
	Very uncomfortable	2 (6%)	1 (3%)
	Slightly uncomfortable	2 (6%)	
	Neutral	3 (10%)	
	Slightly comfortable	7 (23%)	1 (3%)
	Very comfortable	9 (29%)	7 (23%)
	Extremely comfortable	6 (19%)	25 (81%)
Administering rescue breaths with a BVM	Slightly comfortable	2 (6%)	
	Very comfortable	12 (39%)	6 (19%)
	Extremely comfortable	17 (55%)	25 (81%)
Managing an upper airway obstruction	Very uncomfortable	1 (3%)	
	Neutral	2 (7%)	1 (3%)
	Slightly comfortable	12 (40%)	2 (7%)
	Very comfortable	11 (37%)	8 (27%)
	Extremely comfortable	4 (13%)	19 (63%)
Recognizing signs of shock	Slightly comfortable	9 (29%)	
	Very comfortable	13 (42%)	5 (16%)
	Extremely comfortable	9 (29%)	26 (84%)
Providing fluid resuscitation	Neutral	1 (3%)	
	Slightly comfortable	4 (13%)	1 (3%)
	Very comfortable	16 (52%)	4 (13%)
	Extremely comfortable	10 (32%)	26 (84%)
Managing an adult with CHF	Extremely uncomfortable	1 (3%)	
	Very uncomfortable	1 (3%)	
	Slightly uncomfortable	3 (10%)	
	Neutral	8 (26%)	5 (17%)
	Slightly comfortable	13 (42%)	2 (7%)
	Very comfortable	5 (16%)	14 (47%)
	Extremely comfortable		9 (30%)
Ability to rapidly conduct a primary survey	Slightly comfortable	8 (27%)	1 (3%)
	Very comfortable	19 (63%)	10 (32%)
	Extremely comfortable	3 (10%)	20 (65%)
Immobilizing the cervical spine in trauma	Slightly uncomfortable	1 (3%)	
	Slightly comfortable	7 (23%)	1 (3%)
	Very comfortable	11 (35%)	8 (26%)
	Extremely comfortable	12 (39%)	22 (71%)
Managing a woman with vaginal bleeding	Slightly uncomfortable	1 (3%)	
	Neutral	2 (7%)	
	Slightly comfortable	3 (10%)	2 (7%)
	Very comfortable	18 (60%)	13 (43%)
	Extremely comfortable	6 (20%)	15 (50%)

BVM, bag-valve-mask; *CHF*, congestive heart failure.

Table 4. Participants' reported self-efficacy scores before vs after training.

Variable	Pre-test median	Post-test median	P-value
Administering oxygen	7	7	0.01
Placing an airway adjunct	5	7	<0.001
Administering rescue breaths with a BVM	7	7	0.01
Managing an upper airway obstruction	5.5	7	<0.001
Recognizing signs of shock	6	7	<0.001
Providing fluid resuscitation	6	7	<0.001
Managing an adult with CHF	5	6	<0.001
Ability to rapidly conduct a primary survey	6	7	<0.001
Immobilizing the cervical spine in trauma	6	7	0.001
Managing a woman with vaginal bleeding	6	6.5	0.009

BVM, bag-valve-mask; *CHF*, congestive heart failure.

Table 5. Participants' written and simulation-based test scores before vs after training.

Assessment	Pre-training mean % (SD)	Post-training mean % (SD)	Mean difference (SE)	P-value
Written test	66.9 (10.0)	85.0 (7.1)	18.0 (1.7)	<0.001
Simulation (reviewer 1)	41.2 (14.9)	79.9 (11.1)	38.7 (3.6)	<0.001
Simulation (reviewer 2)	43.2 (14.3)	75.8 (13.5)	32.7 (4.1)	<0.001
Simulation (mean)	41.9 (14.2)	78.3 (11.3)	36.3 (3.7)	<0.001

SD, standard deviation; *SE,* standard error.

Participant Feedback

The feedback was overwhelmingly positive with 100% of the participants reporting that the course was "useful." In total, 21 participants (68%) answered that the course was "extremely useful" and the remaining 32% found the course "very useful." The participants indicated that the best part of the course was the medical simulation, particularly the RCDP.

"Simulation as they gave real-life scenarios that we see every day."

"Simulation, scenario, and giving feedback on how [we] performed on scenarios."

"[My favorite part was] guided simulation when we would stop and do a post-mortem of the scenario."

"The simulation part where you have the chance to stop and assess the case."

The participants' recommendations for improving the curriculum varied, but many requested a longer curriculum incorporating other teaching methods.

"More theory before we get to simulations."

"They should add videos to their simulation but everything else was perfect."

"The course should be longer (offered over a number of days) because there is a lot of material to cover."

"Not enough time and next time should be more days to learn more things."

Overall, the participants enjoyed the curriculum and reported that they would be able to incorporate what they had learned from the training into their clinical practice.

"Thank you for your time and teachings. I think I'm well equipped to manage the patient better than before."

"I did have a great and fun time of learning, and I have certainly learned a lot from this course. [I] am going to use what I learned here to save lives."

"… Course was informative and relevant."

"… I have learned a lot from this training. Wish we could regularly do this kind of training."

DISCUSSION

Only limited information is available regarding the development of EMS systems of LMICs. However, based on published literature on LMIC EMS systems, an emphasis is often on transport, rather than on prehospital medical care.[10] A disproportionate number of deaths occur outside the hospital in most LMICs compared to that in high-income countries.[11] As in-hospital emergency care needs are being addressed internationally,[12] efforts to increase the capacity and effectiveness of prehospital providers in LMICs, particularly in medical

intervention, are warranted. We successfully developed and implemented a novel, simulation-based curriculum for prehospital providers in Botswana.[13] To our knowledge, there are no similar training programs regularly used in LMICs to develop the skills of EMS providers.

A majority of providers had not undergone formal training to address prehospital patient care and medical intervention. Interestingly, the mean number of adult resuscitations in the past year (Table 2) of the study was one. Because this is self-reported information, it is unclear whether the providers were not correctly identifying interventions as resuscitations, whether they were adhering more to a "scoop and run" system (simply transporting the patients as fast as they could without emphasizing intervention), whether they abstained from resuscitative efforts due to lack of training, or whether there was some other reason for this low reported value. Nonetheless, participants' prior experiences with resuscitation were low.

We trained 31/46 (67%) of the study-eligible providers in Botswana. Evaluations of the curriculum show that it was an appropriate, effective, and refreshing method of teaching prehospital providers resuscitation and stabilization skills. Overall, the participants reported improved self-efficacy in the topics covered and objectively demonstrated a statistically significant improvement in both written and simulation practical testing. Interestingly, the written test scores did not correspond significantly with self-reported efficacy or simulation test scores post-training (Table 7). Based on our results, a key future investigation would identify and investigate particular clinical outcomes to evaluate the participants' theoretical knowledge (measured by written and simulation testing) measured against in-field performance.

The organizational structure of the Botswana EMS system is similar to many others in sub-Saharan Africa, and the field calls on which the simulation cases were developed correspond with the leading causes of EMS transport in Africa. Although this educational curriculum was specifically developed for use in Botswana, we believe that with minor adjustments it could be customized and applied in prehospital training in other LMIC countries in Africa and perhaps beyond.

This course is an educational tool that we plan to offer regularly throughout the major cities in Botswana as a refresher course for prehospital providers. In addition, our goal is to identify local Botswanan practitioners who have completed the course and are interested in teaching the curriculum independently without the curriculum authors or simulation specialists being present.

LIMITATIONS

This study has a few limitations. First, the study group was a convenience sample based on the availability of EMS workers. As the pool of EMS providers in Botswana is relatively small, this led to a small sample size making it less prudent to

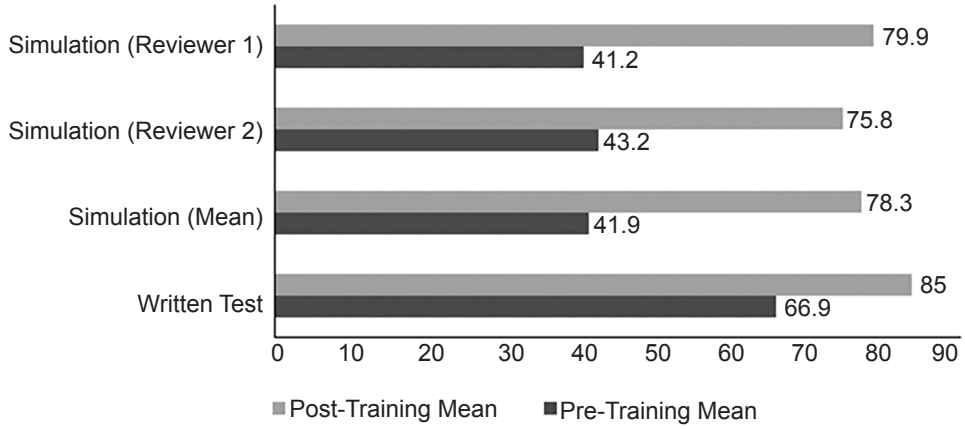

Figure 1. Participants' written and simulation-based test scores before vs after training.

Table 6. Interclass correlation between Reviewer 1 and Reviewer 2.

	Reviewer 1 (pre)	Reviewer 2 (pre)	Reviewer 1 (post)	Reviewer 2 (post)
Reviewer 1 (pre)	1.00			
Reviewer 2 (pre)	0.85***	1.00		
Reviewer 1 (post)	0.03	−0.14	1.00	
Reviewer 2 (post)	0.10	−0.11	0.76***	1.00

Pre, pre-training; *Post*, post-training.
*p < 0.05; **p < 0.01;***p < 0.001

Table 7. Interclass correlation between written test scores, simulation-based test scores, and self-efficacy scores.

	Self-efficacy score (pre)	Self-efficacy score (post)	Written score (pre)	Written score (post)	Simulation score (pre)	Simulation score (post)
[1]Self-efficacy score (pre)	1.00					
[1]Self-efficacy score (post)	0.67***	1.00				
[2]Written score (pre)	0.34	0.33	1.00			
[2]Written score (post)	−0.13	−0.01	0.40*	1.00		
[3]Simulation score (pre)	0.47*	0.40*	0.41*	−0.03	1.00	
[3]Simulation score (post)	0.25	0.24	−0.19	−0.05	−0.07	1.00

*p < 0.05, **p < 0.01, ***p < 0.001

[1]Mean score across items on participant-reported self-efficacy survey; [2]mean score on written test; [3]mean score across Reviewers 1 and 2 on simulation-based scenarios.

compare intervention and control groups. In addition, many participants were dissatisfied with the short duration of the course and requested that it be longer and cover more topics. This is an opportunity to integrate and offer a concomitant simulation-based curriculum with this course. The course lasted for two days and evaluated pre- and post-testing one day apart. Retention of knowledge could have been re-evaluated several weeks or months after the course to obtain longer-term outcome data. We did our best to account for inter-rater variability when reviewing the video footage and subject evaluations; however, there is always potential for human error.

This was an educational study, which addressed the need for training; however, it did not address other system deficiencies. Similarly, Botswana is a middle-income country with limited resources designated for the EMS system. Although we considered the inventory of typical resources to design our education program, we did not evaluate how lack of resources affects the care provided. Rather, we focused on ensuring that the providers knew what resources were available to them and how they could be used. The focus of this study was not to evaluate the retention of knowledge, practice changes, or clinical outcomes resulting from this curriculum. However, researchers are currently evaluating whether the skills taught in this curriculum are affecting prehospital providers' practice by reviewing patient report forms that note exactly what was done by prehospital providers in each actual patient field response. Preliminary results suggest that there has been a significant increase in the completion of tasks (evaluations and/or interventions).[14] The researchers can also compare the actions of those who participated in the course with those who did not, and for those who did participate in this training, patient care interventions can be compared before and after the training.

CONCLUSION

Prehospital medicine continues to develop and expand around the world, particularly in LMIC countries in sub-Saharan Africa. This simulation-based course was a novel and effective way to educate providers in Botswana on prehospital resuscitation. Future efforts should be directed toward evaluating longer-term retention of participant knowledge and evaluating behavioral changes of providers based on application of the curriculum concepts and how these applications affect patient outcomes. Although this study did not have a control group, future investigations could compare the patient outcomes of our course participants against those who did not participate considering that the participants were derived strictly from a pool of off-duty nurses and EMTs. At the time of this study, there was no formal training for Botswana EMS recruits. We plan to offer this course regularly; however, it is not compulsory. This curriculum could potentially be regularly used as an introductory course in prehospital resuscitation and as a refresher for those who may not be performing many prehospital, medical resuscitations in their practice.

The curriculum described in the present study represents a valuable educational tool that serves to educate healthcare providers, disseminate practical knowledge, and standardize clinical procedures. Implementing the concepts taught in this course could potentially advance prehospital medical care and patient outcomes not only in Botswana but also in other resource-limited environments.

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Conflicts of Interest: By the WestJEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. Funding for this training program was provided by an education award from Baylor College of Medicine, Department of Pediatrics and Texas Children's Hospital.

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Prevalence of Post-Traumatic Stress Disorder in Emergency Physicians in the United States

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Section Editor: Patrick Maher, MD
Submission history: Submitted February 5, 2019; Revision received July 11, 2019; Accepted July 12, 2019
Electronically published August 28, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.42671

Introduction: There is increasing concern about the effects of occupational stressors on the wellness of healthcare providers. Given high patient acuity, circadian rhythm disruption, and other workplace stressors, emergency physicians (EP) would be predicted to have high rates of occupational stress. We conducted this study to assess the prevalence of post-traumatic stress disorder (PTSD) in attending EPs practicing in the United States.

Methods: A link to an electronic questionnaire was distributed through the emergency medicine-centric publication *Emergency Medicine News*. We compared the prevalence of PTSD in EPs to the general population using a chi-square goodness of fit test, and performed logistic regression to assess for significance of risk factors.

Results: We received survey responses from 526 persons. In this study, EPs had a PTSD point prevalence of 15.8%. Being a victim of a prior trauma or abuse is the primary predictor of PTSD (odds ratio [OR] [95% confidence interval {CI}, 2.16 (1.21 – 3.86)], p = 0.009) and PTSD severity score (OR [95% CI, 1.16 (1.07 – 1.26)], p <0.001).

Conclusion: Emergency physicians have a substantial burden of PTSD, potentially jeopardizing their own health and career longevity. Future studies should focus on identifying subgroups at higher risk for PTSD and modifiable risk factors. Prevention and treatment strategies should be developed and tested in healthcare providers. [West J Emerg Med. 2019;20(5)740-746.]

INTRODUCTION

Post-traumatic stress disorder (PTSD) affects some people who have been exposed to traumatic events such as military action, natural disasters, sexual violence, or serious illness/injury. In the United States (U.S.), the point prevalence of PTSD in adults is estimated to be 3.8%. The diagnosis of PTSD requires an exposure to trauma and symptoms from multiple domains, including intrusive memories, avoidance, negative mood, and hyperarousal. Symptoms must occur for more than one month and cause functional impairment to meet criteria for PTSD. Exposure was originally defined as personal experience, witnessing events, or indirect exposure through events that occurrred to loved ones.

The terms secondary traumatic stress (STS) and compassion fatigue were used to describe the emotional toll suffered by persons who have repeated but indirect exposure to trauma as part of their professional or volunteer duties, such as healthcare workers, firefighters, forensic examiners, and humanitarian workers. In recognition of a growing body of literature suggesting STS has a profound effect on workers in these fields, the 2013 update to the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5) added repeated indirect

exposure as an exposure class.

Physicians have high rates of substance abuse and suicide, which may be mediated by underlying PTSD.[6-8] STS and PTSD have been described in many types of healthcare providers, but emergency physicians (EP) may be particularly vulnerable. EPs deal with multiple challenges such as the potential to witness death and trauma on a frequent basis, diagnostic uncertainty, high patient acuity, crowding, and circadian rhythm disruption that place them as elevated risk for occupational stress. A single-site study from the U.S. found that 11.9% of emergency medicine (EM) residents met criteria for PTSD, with 30% having symptoms that did not meet the threshold for diagnosis.[9] A study of EPs and advance practice providers from a group practice in the U.S. found a PTSD prevalence of 12.7%.[10] Research from other countries corroborates this vulnerability, with prevalence of self-assessed PTSD of 16.8% in German EPs, 15.4% in Pakistani EPs, and 14.5% in Belgian EPs.[11-13]

The objective of this study was to determine the point prevalence of PTSD in a cohort of practicing EPs from multiple practice settings in the U.S., and to compare this to the prevalence in the general population. The secondary objective was to determine if personal or practice-related factors mediate prevalence of PTSD. Determining the prevalence of PTSD in EPs and identifying high-risk subgroups will hopefully improve methods to prevent and treat PTSD in EPs and other healthcare providers.

Population Health Research Capsule

What do we already know about this issue?
Emergency physicians have multiple occupational stressors that may increase their risk for post-traumatic stress disorder (PTSD). Previous single site studies have found a prevalence of 12-13% in emergency medicine practitioners.

What was the research question?
Using a validated screening tool, the study aimed to determine the point-prevalence of PTSD in emergency physicians from the United States who practice in a variety of settings.

What was the major finding of the study?
The point prevalence of PTSD in emergency physicians is 15.8%. A history of prior exposure to trauma was the only independent risk factor for meeting the screening threshold for PTSD.

How does this improve population health?
Understanding the magnitude of the problem and risk factors for development of PTSD will hopefully drive development of interventions to reduce occupational stress in emergency physicians

METHODS

Study Design

We developed a questionnaire using a validated PTSD screening tool (Appendix 1) and demographic factors predicted to mediate risk, based on a review of the literature.14 A short background article with a recruitment statement and a link to the electronic survey was distributed through *Emergency Medicine News*. The survey was advertised once in December 2015 and was open for completion through April 2016. Completion of the survey was entirely voluntary and anonymous. The online survey company (Qualtrics, Provo, Utah) collected the data and forwarded results to the research team. The study protocol was approved by the Institutional Review Board at Saint Louis University.

Selection of Participants

Participants were voluntary and self-selected from the readership of *Emergency Medicine News*. The newsletter is distributed free of charge to practicing (postgraduate) EPs. The recruitment statement specified that respondents should be practicing EPs; there were no exclusion criteria listed. We attempted to prevent duplication of participants by electronically collecting participant data and computer internet protocol numbers. Once this data was recorded, the survey would not re-open for the same data and computer internet protocol numbers.

Methods and Measurements

The PTSD screening tool, PTSD Checklist – Civilian Version (PCL-C) (Appendix 1), was entered into an online survey tool. It consists of 17 questions that are answered on a five-point Likert scale, based off of experiences in the prior month. From this survey we calculated a total PTSD severity score (range = 17-85) and defined PTSD according to the DSM criteria, which was a symptomatic response to at least 1 "B" item, at least 3 "C" items, and at least 2 "D" items. Symptomatic responses were defined as those in the categories of "Moderately" or above (3 on Likert scale of 1-5).[1] The PCL-C has been validated as a screening tool as well as an adjunct to the clinical interview for the diagnosis of PTSD, with an estimated sensitivity of 0.70, specificity of 0.90, and a positive likelihood ratio of 6.8.[15-16]

Additional covariates we collected included gender, age (22 – 28, 29 – 35, 36 – 42, 43 – 49, 50 – 56, 57 – 63, 63 – 70, > 70 years); board certification (EM, family practice, internal medicine and pediatrics); years of service (0 – 5, 6 – 11, 12 – 17, 18 – 23, 24 – 29, > 29 years); location of work (urban, suburban, or rural); trauma level status (I, II, III, IV, or "None"); military experience (yes/no); marital status (single, married or domestic partner); whether they had children (yes/no); and whether they were a prior victim of trauma or abuse (yes/no).

Statistical Analysis

We used descriptive statistics to analyze participants' demographic characteristics, their overall PTSD severity score, and whether or not they met criteria for diagnosis of PTSD. Chi-square goodness of fit test was used to determine whether the prevalence of PTSD in EPs was similar to that of the general population.

Independent samples t-tests, one-way analysis of variance (ANOVA) tests and Spearman correlations were used to assess the association between dichotomous, multi-categorical, and ordinal patient characteristics, respectively, with total PSTD score. In the case of a significant ANOVA test, we applied Bonferroni corrections to adjust for multiple significance testing in the post hoc tests. We assessed bivariate analysis of the ordinal characteristics, age, years of service, and trauma level with whether or not the patient had PTSD using Kruskal-Wallis tests, while categorical characteristics used the chi-square test. We conducted a multiple linear regression on the outcome of the natural log of PTSD score to assess potential predictors of score and a multiple logistic regression on whether or not the subject had PTSD. For both outcomes we conducted bivariate regressions on each characteristic, and if the characteristic had a p value <0.20, we then included it in the multivariate regression model. Due to low counts, categories of some characteristics were combined to increase the count. We performed analyses using SPSS Statistics for Windows version 23 (IBM Corp., Armonk, NY). Statistical tests were two-tailed and the significance level set at $p < 0.05$.

RESULTS

Table 1 shows the demographic characteristics of the study participants. There were 526 participants in the study with 56.1% males, 82.3% married, and approximately 50% having less than 11 years of service. Those who reported being a victim of trauma or abuse made up 15.8% of the participants. The majority of respondents worked in suburban or urban locations.

The breakdown of the components of the PTSD severity score as well as the total PTSD severity score are listed in Appendix 2. Difficulty falling or staying asleep was the most common criterion of PTSD that the subjects reported being bothered by during the prior month, with 37 (7%) reporting being extremely bothered. The mean total PTSD score was 31.1 (standard deviation [SD] =11.7). Of the total sample, 83 (15.8%) met criteria for a diagnosis of PTSD according to the DSM-5. This is significantly higher than the prevalence of PTSD in the general population (point prevalence 3.8%, p<0.001).

The relationship between demographic covariates, total PTSD severity score, and meeting criteria for PTSD are shown in Table 2. The mean (SD) PTSD score for those who reported being a victim of trauma or abuse was 35.9 (14.0), statistically different than that of non-victims 30.2 (11.0), p = 0.001. Bivariate analysis showed no statistically significant difference between mean PTSD severity score by age, gender, marital status, having children, or military service. Those who met the DSM criteria for PTSD tended to be older, median (interquartile range [IQR]) PTSD: 43-49 years (43-49 years – 50-56 years) vs. no PTSD: 36 – 42 years (26-42 years – 50-56 years), p =0.001. Subjects who met criteria for PTSD were also more likely to have served in the military (20.5% vs 11.1%, p = 0.017). Subjects with prior trauma had a higher risk for meeting the criteria for PTSD than those without prior trauma (28.9% vs 13.3%, p<0.001).

The influence of workplace variables, total PTSD severity score, and meeting criteria for PTSD is shown in Table 3. We found no significant correlation between years of service, or being board certified in EM, family medicine or internal medicine, and the PTSD severity score. Those who were board certified in pediatric medicine had a lower mean (SD) PTSD severity score than those not certified 24.7 (7.8) vs 31.3 (11.8), (p = 0.04). In addition, there was a weak but significant correlation between facility trauma level and PTSD severity score ($r_s = 0.12$, p = 0.006). The median (IQR) of years of service was 12-17 years (6-11 years – 24-29 years) for those with PTSD and 6-11 years (6-11 years – 18-23 years) for those without PTSD, p = 0.003.

Appendix 3 shows relationships between predictor variables and PTSD severity score in the multivariate model. After adjusting for age, marital status, military service, being a victim of a past trauma, trauma level at practice site, location of work, being board certified in EM, and being board certified in pediatric medicine, only being a victim of a past trauma and hospital trauma level were significant predictors of PTSD severity score. Prior victims had a 16% increase in PTSD severity score (95% confidence interval [CI], 7-26%, p <0.001), and those working at a trauma level II hospital had a 10% increase in PTSD severity score (95% CI, 1-20%, p = 0.03) compared to those working at a level I trauma center or those working at trauma level III/IV hospitals.

Predictors of meeting criteria for PTSD can be found in Appendix 4. After adjusting for age, gender, marital status, prior military service, being a victim of a previous trauma, years of service, and being board certified in EM, only being a victim of a previous trauma was a significant predictor of PTSD. Those who were a victim were more than twice as likely to be diagnosed with PTSD as those who were not a victim (odds ratio OR = 2.16, 95% CI, 1.21 – 3.86, p = 0.009).

DISCUSSION

In this study, the point prevalence of self-assessed PTSD in EPs was 15.8%. PTSD severity scores were higher among victims of prior trauma and physicians working at trauma level II hospitals. Greater age, prior military service, increased years of service, and a history of prior victimization were associated with meeting the criteria for PTSD. However, being a victim of prior trauma was the only significant risk factor for PTSD in the multivariate model.

Prevalence of PTSD among resident physicians in the U.S. ranges from 5.2% in medicine and pediatrics, to 22% in surgical residents and 29% in EM residents.[17-20] Intensivists, who deal with many of the same occupational stressors as EPs, have a

Table 1. Characteristics of physician participants, n = 526, in study examining prevalence of post-traumatic stress disorder.

Demographic Factors	n (%)	Demographic Factors	n (%)
Age groups (years)		Location of work	
22-28	5 (1.0)	Urban	221 (42.0)
29-35	109 (20.7)	Suburban	243 (46.2)
36-42	146 (27.8)	Rural	62 (11.8)
43-49	95 (18.1)	Trauma	
50-56	85 (16.2)	One	141 (26.8)
57-63	61 (11.6)	Two	150 (28.5)
63-69	23 (4.4)	Three	92 (17.5)
70+	2 (0.4)	Four	23 (4.4)
Gender		None	120 (22.8)
Male	295 (56.1)	Military	
Female	230 (43.7)	Yes	66 (12.5)
Unknown	1 (0.2)	No	460 (87.5)
Board EM		Marital status	
Yes	488 (92.8)	Married	433 (82.5)
No	38 (7.2)	Domestic partner	15 (2.9)
Board Family Medicine		Single	78 (14.8)
Yes	17 (3.2)	Children	
No	509 (96.8)	Yes	419 (79.7)
Board Internal Medicine		No	107 (20.3)
Yes	23 (4.4)	Victim	
No	503 (95.6)	Yes	83 (15.8)
Board Pediatrics		No	443 (84.2)
Yes	14 (2.7)		
No	512 (97.3)		
Years of service			
0-5	118 (22.4)		
6-11	149 (28.3)		
12-17	89 (16.9)		
18-23	67 (12.7)		
24-29	57 (10.8)		
30+	46 (8.7)		

EM, emergency medicine.

reported PTSD prevalence of 13%.[21] In one study, surgeons had a PTSD prevalence of 15% while trauma surgeons had a prevalence of 17%, not significantly different.[22] A survey of trauma surgeons using the PCL-C found symptoms of PTSD in 40%; 15% met criteria for PTSD. In that study, PTSD symptoms were higher in male surgeons, surgeons who had more operative cases, surgeons who had more than seven call shifts per month, and those who designated less time for relaxation. Development of PTSD was higher in surgeons managing more than five critical cases per call.[23]

PTSD is associated with professional quality of life, burnout, intent to change careers, risk of occupational injury, and markers of provider health such as sleep quality and obesity.[24-26] There is increasing evidence that burnout and PTSD among providers worsen patient outcomes.[27-28]

Not all persons who suffer a trauma develop symptoms of PTSD. Risk factors for development of PTSD in the general population include underlying psychiatric problems, concurrent medical illness, history of being a victim of child abuse, higher degree of acute stress symptoms, and more severe trauma as

the inciting event.[29-31] Psychological traits of neuroticism and dissociation, use of maladaptive coping strategies such as disengagement, and cognitive factors such as self-perceived resilience and suppression of emotion predicted a higher risk of developing PTSD in newly trained paramedics.[32] Potential healthcare-specific risk factors for PTSD include workplace violence, bullying, the death of a child, fear of exposure to infectious disease, litigation stress, use of electronic health records, long work hours, and circadian disturbance due to night shifts.[18, 27-28, 33-35] Bellolio et al. found that working primarily night shifts and working more than 80 hours per week were predictive of burnout, but found no increased risk based on specialty when these factors were controlled.[36]

One surprising finding in this study was that physicians who practiced in level II trauma centers had a higher PTSD scores than physicians working in either level I centers or level III/IV centers. It might be predicted that physicians working in facilities with a lower burden of severe trauma would have a lower prevalence of PTSD; thus, the mechanism for higher PTSD scores in physicians at level II centers is unclear. We postulate that shared responsibility with in-house trauma surgeons and the availability of other resources not found at level II hospitals may be protective for physicians at level I hospitals. Total hours worked per month and other scheduling factors may also vary between level I and II hospitals. To our knowledge, this has not been reported previously.

There are also protective factors that may prevent development of PTSD. Having good family and workplace support are the most important, but use of light-hearted humor and adaptive coping strategies are also protective.[37-42] A strong professional identity is important for resilience; however, one study suggested a higher sense of calling may be hazardous to practitioners exhibiting early signs of PTSD.[43-44]

Current research suggests that job burnout precedes development of PTSD; thus, interventions to increase resilience and reduce burnout should ameliorate the prevalence of PTSD in healthcare workers.[45] Research in rescue workers suggests that early symptoms of emotional distress predict long-term sequelae.[46] Most resilience interventions in healthcare workers are based on mindfulness training or cognitive behavioral therapy.[47] Studies of resilience training in EM have shown mixed results.[48-49] While personal resilience is important to prevent burnout and PTSD, a recent systematic review and meta-analysis of programs to reduce burnout in physicians suggests that focusing on adaptations to the work environment are more effective than interventions that target individual providers.[50] Noben et al found that an intervention to improve mental health among hospital staff was cost-effective.[51]

LIMITATIONS

Limitations include the small number of respondents to the survey. *Emergency Medicine News* reported a readership of 38,909 during that time frame (personal communication, Wolters Kluwer). People are more likely to respond to surveys if the topic is of personal interest, eg, because they are affected by the items asked about. People who respond almost certainly have different characteristics than those who do not, causing selection bias.[51] However, the prevalence of self-assessed PTSD in our study was similar to the prevalence reported in multiple other countries. To the best of our knowledge, this study is the largest multisite study to assess the prevalence of PTSD in EPs in the United States.

Although the EM news magazine is primarily distributed to practicing physicians, it is possible that residents, medical students, or other healthcare providers may have seen the survey link and responded. The term "prior victim of trauma or abuse" was not specifically defined, which may have resulted in some mis-categorization. Additionally, this survey could not determine the contribution of work-related stressors to the baseline prevalence of PTSD in EPs. Like many highly stressed professionals who are under constant scrutiny, EPs may not report symptoms of PTSD. Having PTSD may be perceived as a weakness or inability to do one's job. There may be fears that once diagnosed, hours may be cut back or one may be re-assigned to less-stressful work areas. This can lead to loss of self-confidence and respect.

CONCLUSION

There is a substantial burden of PTSD among practicing emergency physicians. Additional large-scale studies should be done to more accurately assess the prevalence of PTSD symptoms in EPs, modifiable risk factors for development of PTSD, the relationship between PTSD, burnout, and career longevity, and the effects of interventions currently underway within the specialty. Interventions at the organizational level should be prioritized**.**

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Concurrent Proximal Fractures Are Rare in Distal Forearm Fractures: A National Cross-sectional Study

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Section Editor: Patrick Maher, MD
Submission history: Submitted March 3, 2019; Revision received August 6, 2019; Accepted May 30, 2019
Electronically published August 26, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.5.42952

Introduction: Distal forearm fractures (DFF) account for 1.5% of emergency department (ED) visits in the United States. Clinicians frequently obtain imaging above/below the location of injury to rule out additional injuries. We sought to determine the incidence of associated proximal fractures (APF) in the setting of DFF and to evaluate the imaging practices in a nationally representative sample of EDs.

Methods: We queried the 2013 National Emergency Department Sample using International Classification of Diseases, 9th edition, diagnostic codes for DFF and APF. Current Procedural Technology codes identified associated imaging studies. We calculated national estimates using a weighted analysis of patient and hospital-level characteristics associated with APF and imaging practices. An analysis of costs estimated the financial impact of additional imaging in patients with DFF using Medicare reimbursement to approximate costs according to the 2018 Medicare Physician Fee Schedule.

Results: In 2013, an estimated 297,755 ED visits (weighted) were associated with a DFF, of which 1.6% (4836 cases) had an APF. The incidence of APF was lower among females (odds ratio [OR] (0.76); 95% confidence interval [CI], 0.64-0.91) but higher in metropolitan teaching hospitals compared to metropolitan non-teaching hospitals (OR [2.39]; 95% CI, 1.43-3.99) and Level 1 trauma centers (OR [3.9]; 95%, 1.91-7.96) compared to non-trauma centers. Approximately 40% (n = 117,948) of those with only DFF received non-wrist radiographs and 19% (n = 55,236) underwent non-wrist/non-forearm imaging. Factors independently associated with additional imaging included gender, payer, patient and hospital rurality, hospital region, teaching status, ownership, and trauma center level. Nearly $3.6 million (2018 U.S. dollars) was spent on the aforementioned additional imaging.

Conclusion: Despite the frequency of proximal imaging in patients with DFF, the incidence of APF was low. Further study to identify risk factors for APF based on mechanism and physical examination factors may result in reduced imaging and decreased avoidable healthcare spending. [West J Emerg Med. 2019;20(5)747-759.]

INTRODUCTION

Distal forearm fractures (DFF) are some of the most common fractures evaluated and treated in the United States, and this incidence has been increasing over the last 50 years.[1-5] DFFs account for roughly 1.5% of emergency department (ED) visits annually[3] with complications including chronic pain, osteoarthritis, median nerve compression, loss of motion, and complex regional pain syndrome.[6,7] Most injuries are due to minor trauma such as accidental falls, especially in the geriatric population.[1,3,8] With an aging population, the Medicare costs for treating these fractures are also increasing. In 2007, $170 million (United States dollars) in payments were made by Medicare for distal radius fractures alone.[9] Many clinicians have been taught that elbow imaging should be a component of the evaluation of DFF to avoid missing corresponding injuries; however, there is a lack of primary literature to support this practice.[10]

Excessive imaging continues to lead to additional expense and radiation risk, and the Choosing Wisely Campaign has targeted low-value imaging as one of its priorities in reducing unnecessary healthcare spending.[11] Describing the epidemiology and fracture patterns of DFF and associated proximal fractures (APF) could better target imaging to those most likely to benefit, and clinical decision rules could be developed to target imaging practices toward high-risk groups. The objectives of this study were the following: 1) to determine the proportion of concurrent APF in the setting of DFF; 2) to better understand the current imaging practice used in EDs to evaluate patients with DFF; 3) to perform a cost analysis on current imaging practices; and 4) to identify factors associated with APF among those with DFF.

Population Health Research Capsule

What do we already know about this issue?
Routine imaging proximal to the site of a distal forearm fracture is often taught; however, the incidence of proximal fractures is limited to case reports.

What was the research question?
How frequently do those with distal forearm fractures have additional proximal fractures?

What was the major finding of the study?
In patients with distal forearm fractures, an associated proximal fracture occurs 1.6% of the time.

How does this improve population health?
Understanding the epidemiology of fracture patterns can lead to more targeted and cost-effective evaluations of patients.

METHODS

Study Design, Setting, and Population

We conducted a cross-sectional study of data from the 2013 National Emergency Department Sample (NEDS), a dataset of a representative sample of U.S. ED visits developed by the Healthcare Cost and Utilization Project.[12] NEDS is a sample comprised of discharge data for ED visits across more than 900 hospitals located in 33 states and the District of Columbia. The data approximate a 20% stratified sample of U.S. hospital-based EDs with over 30 million ED visits annually, with a weighted estimate of 135 million ED visits. We included all records with DFF, defined by the *International Classification of Disease*s, 9th edition, (ICD-9) codes 813.4-813.47, 813.5-813.54, 833.01. We excluded records with a discharge diagnosis consistent with DFF but without any imaging recorded, and we excluded visits requiring inpatient admissions.

This study was determined not to qualify as human subjects research by the local institutional review board and is reported in accordance with the Strengthening Observational Studies in Epidemiology (STROBE) publication guideline.[13]

Definitions

DFF was defined through a series of ICD-9 codes (Supplemental File, Appendix A). Three independent experts in the management of DFFs identified ICD-9 codes that were "definitely" DFFs, codes that "could include" DFFs, and codes that were "not" DFFs. We used the most conservative "definite" definition of DFF (ie, the specific ICD-9 codes categorized as DFF obviously entailed a fracture in the distal part of the extremity), and other definitions were used for sensitivity analyses (Figure 1). We defined APFs as all other non-DFFs of the upper extremity. Other fractures of the upper extremity (humerus and elbow), as well as unspecified portions of the forearm, were categorized as APF in this conservative "definite" definition of DFF. We defined imaging as having a claim for a procedure code for imaging of the upper extremity, identified through Current Procedural Terminology (CPT)-4 codes (Supplemental Content, Appendix B). When evaluating for a DFF, we considered standard imaging to be of the wrist or forearm, while non-standard imaging was defined as imaging procedures performed at non-wrist and non-forearm sites (ie, elbow and humerus).

Cost Analysis

We estimated healthcare costs from a societal perspective of healthcare spending alone. The societal cost of the additional imaging procedures was approximated by the Medicare reimbursement rate. For the cost analysis, additional imaging was defined as a three-view elbow radiograph in

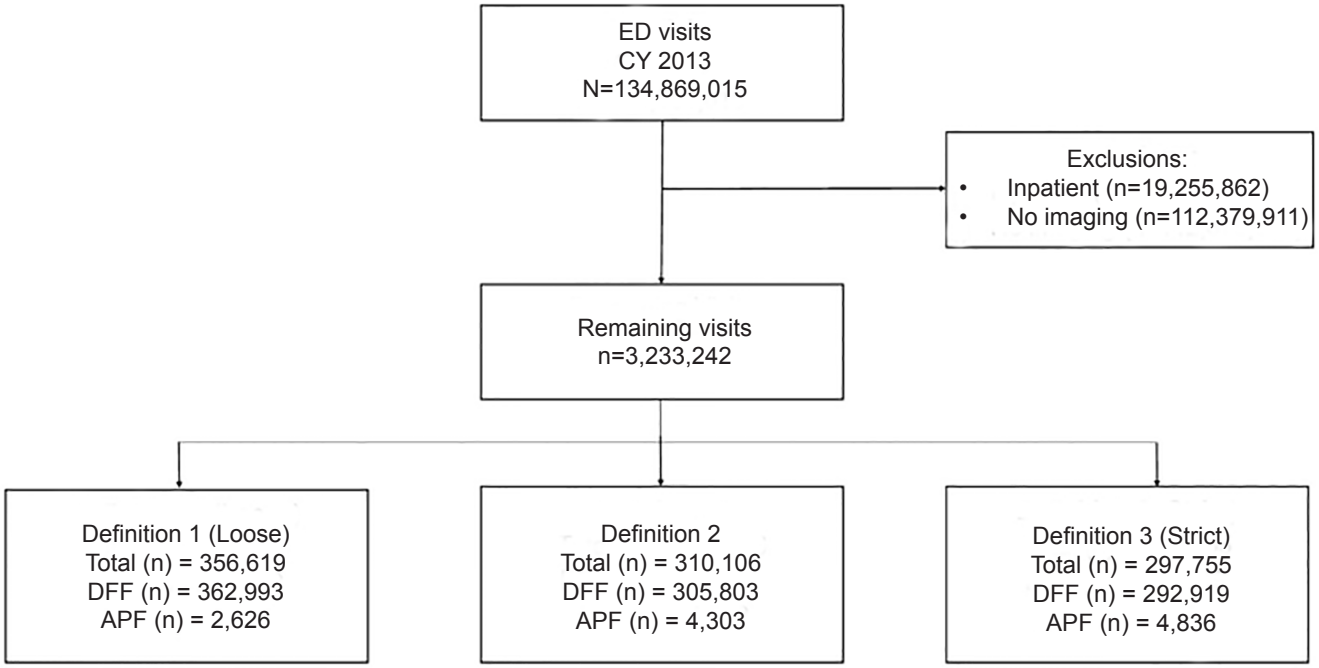

Figure 1. Flowchart of sample selection, National Emergency Department Sample 2013.
ED, emergency department; *DFF*, distal forearm fracture: represents the number of records with DFF only; *APF*, associated proximal fracture: represents the number of records with APF among those who have a DFF.

the ED, and costs were estimated using CPT-4 code 73080 (radiograph of the elbow, minimum of three views). The cost of imaging was estimated using the 2018 Hospital Outpatient Prospective Payment System for the technical component and the 2018 Medicare Physician Fee Schedule for the professional component. The cost for one additional image, defined as one three-view elbow radiograph in the ED, was estimated to be $71.28. All costs are reported in 2018 $USD.

We used a decision analysis model incorporating estimated base parameters (ie, prevalence of DFFs) and probability of APF, given DFF was used to estimate the population healthcare cost of imaging DFFs without APF. Finally, to account for potential variation in the actual cost of the additional imaging by facility, state, and payer, we performed a sensitivity analysis varying the cost by 75% and 150%. These differences were determined by the reported magnitude of differences in commercial insurance and Medicaid reimbursement compared to Medicare reimbursement.[14,15]

Outcomes of Interest

The primary outcome of interest was the incidence of APF among patients with DFF. The secondary outcome was the proportion of patients with DFF who had non-standard imaging performed.

Statistical Analysis

To identify factors associated with APF we compared patient and hospital-level characteristics between DFF patients with and without APF, using weighted estimates. We conducted a bivariate analysis using variables in NEDS for primary sampling units, weights, and clustering to account for the sampling strategy and frame for this dataset. To ensure limiting this dataset would not introduce any bias, we evaluated the DFF subset with and without imaging across several patient and facility characteristics (Table 1). We then assessed differences in patient or hospital-level characteristics of visits vs those with standard vs non-standard imaging (univariate logistic regression, OR [odds ratio], 95% confidence interval [CI]). We included all patient and hospital-level characteristics in the final multivariate logistic model. Collinear variables were removed individually with those removed being ones of lower priority. As part of a sensitivity analysis, we evaluated whether a change in the definition of DFF and APF would influence the model estimates for each individual- and facility-level covariate.

We performed data management and statistical analysis using SAS v.9.4 (SAS Institute, Cary, NC), on a Unix-based institutional distributed computing cluster (High-Performance Computing, Information Technology Services, University of Iowa, Iowa City, IA).

RESULTS

Demographics

There were 464,597 visits indicating DFF, of which 166,842 (36%) were excluded for incomplete reporting with no CPT-coded imaging (eg, may have been transferred and had imaging performed elsewhere or had CPT codes incompletely reported) (Table 1). The final sample analyzed included 297,755 visits with DFF identified. Demographic characteristics for excluded records

Table 1. Characteristics of population with distal forearm fractures, National Emergency Department Sample 2013.

Patient or facility characteristics	DFF with imaging (weighted n =297,755)		DFF without imaging (weighted n =166,842)	
	Weighted N	% (95% CI)	Weighted N	% (95% CI)
Patient characteristics				
Age (years)				
< 18	131,666	44.2 (42.2-46.2)	80,395	48.2 (42.1-54.3)
18-44	41,879	14.1 (13.3-14.8)	23,222	13.9 (12.1-15.7)
45-64	62,573	21.0 (20.2-21.9)	31,321	18.8 (16.4-21.1)
≥65	61,637	20.7 (19.8-21.6)	31,904	19.1 (16.8-21.4)
Sex				
Male	132,717	44.6 (43.7-45.4)	76,781	46.0 (44.2-47.8)
Female	165,024	55.4 (54.6-56.3)	90,058	54.0 (52.2-55.8)
Payer				
Medicare	60,089	20.2 (19.2-21.2)	32,227	19.4 (17.0-21.7)
Medicaid	66,602	22.4 (21.0-23.8)	37,647	22.6 (20.5-24.8)
Self-pay	29,330	9.9 (9.1-10.6)	17,247	10.4 (9.1-11.7)
No charge	1,605	0.5 (0.3-0.7)	366	0.2 (0.1-0.3)
Other	17,060	5.7 (5.1-6.3)	9,126	5.5 (4.4-6.6)
Private (including HMO)	122,618	41.2 (39.7-42.8)	69,819	42.0 (38.7-45.2)
Patient residence rurality				
Large central metropolitan	70,215	23.8 (20.3-27.3)	46,832	28.2 (22.4-34.0)
Large fringe metropolitan	80,944	27.5 (24.1-30.9)	25,697	15.5 (11.8-19.1)
Medium metropolitan	58,027	19.7 (16.6-22.8)	44,234	26.6 (21.3-32.0)
Small metropolitan	22,246	7.5 (5.7-9.4)	18,239	11.0 (8.0-14.0)
Micropolitan	38,064	12.9 (11.4-14.4)	19,078	11.5 (9.1-13.9)
Not metropolitan or micropolitan	25,333	8.6 (7.5-9.7)	11,994	7.2 (5.8-8.7)
Facility characteristics				
Hospital urban-rural location				
Large metropolitan	142,018	47.7 (44.2-51.2)	66,579	39.9 (31.9-47.9)
Small metropolitan	74,894	25.2 (22.1-28.2)	62,489	37.5 (31.0-43.9)
Micropolitan	37,132	12.5 (10.3-14.6)	18,207	10.9 (8.0-13.8)
Not metropolitan or micropolitan	22,682	7.6 (6.3-8.9)	10,750	6.4 (4.2-8.8)
Collapsed category of small metropolitan and micropolitan	7,577	2.5 (1.1-3.9)	3,993	2.4 (0.8-4.0)
Metropolitan, collapsed category of large and small metropolitan	7,030	2.4 (1.2-3.5)	4,394	2.6 (0.3-5.0)
Non-metropolitan, collapsed category of micropolitan and rural	6,423	2.2 (1.9-2.4)	431	0.3 (0.0-0.6)
Hospital region				
Northeast	65,623	22.0 (19.3-24.7)	13,160	7.9 (4.9-10.9)
Midwest	56,898	19.1 (16.6-21.6)	56,005	33.6 (25.3-41.9)
South	128,061	43.0 (39.5-46.5)	32,077	19.2 (15.0-23.5)
West	47,172	15.8 (12.9-18.8)	65,600	39.3 (32.6-46.0)

Table 1. Continued.

Patient or facility characteristics	DFF with imaging (weighted n =297,755)		DFF without imaging (weighted n =166,842)	
	Weighted N	% (95% CI)	Weighted N	% (95% CI)
Hospital control/ownership of hospital				
Government or private, collapsed category	183,491	61.6 (58.4-64.9)	107,984	64.7 (58.6-70.8)
Government, nonfederal, public	24,665	8.3 (6.4-10.1)	8,534	5.1 (2.9-7.4)
Private, non-profit, voluntary	52,016	17.5 (14.9-20.1)	31,050	18.6 (14.0-23.3)
Private, investor-own	25,907	8.7 (7.4-10.0)	10,419	6.2 (4.3-8.2)
Private, collapsed category	11,676	3.9 (2.9-4.9)	8,854	5.3 (3.3-7.3)
Teaching status of hospital				
Metropolitan non-teaching	118,975	40.0 (36.7-43.2)	69,734	41.8 (35.0-48.5)
Metropolitan teaching	112,544	37.8 (34.0-41.6)	67,720	40.6 (32.6-48.6)
Non-metropolitan hospital	66,236	22.2 (19.8-24.7)	29,387	17.6 (13.8-21.5)
Hospital trauma center level				
Non-trauma center	129,327	43.4 (40.0-46.9)	72,035	43.2 (36.4-50.0)
Trauma Level I	44,024	14.8 (11.6-18.0)	25,717	15.4 (5.9-24.9)
Trauma Level II	25,171	8.5 (6.1-10.8)	20,677	12.4 (8.6-16.2)
Trauma Level III	25,711	8.6 (6.7-10.6)	21,177	12.7 (8.9-16.5)
Non-trauma or trauma Level III	59,847	20.1 (17.8-22.4)	22,202	13.3 (9.7-16.9)
Trauma Level 1 or II, collapsed	13,675	4.6 (3.6-5.6)	5,034	3.0 (1.2-4.8)

DFF, distal forearm fracture; *CI,* confidence interval; *HMO*, health maintenance organization.

were similar to the included records. The majority of patients with DFF were <18 years (44.2%), female (55.4%), and had private insurance (41.2%) (Table 2).

Distal Radius and Associated Proximal Fractures

The number of DFF records with APF was 1.6% (n = 4836, 95% CI, 1.2-2.1%) with the majority of the APF being radial shaft fractures (15.2%), radial head fractures (14.9%), and supracondylar humerus fractures (12.9%) (Table 3). Although these were the most common APF they were still exceedingly rare in those with DFF, with radial shaft fractures occurring in 0.56%, radial head fractures occurring in 0.55%, and supracondylar humerus fractures occurring in 0.48% of patients with DFF (Table 3). Among those with a DFF, the odds of APF was lower among those age >65 years compared to those <18 years (unadjusted [u] OR [0.59]; 95% CI, 0.41-0.86) (Table 2). The unadjusted odds of APF were also lower among females compared to males, (uOR [0.76]; 95% CI, 0.64-0.91). Patients seen in metropolitan teaching hospitals had higher odds of APF being diagnosed than those in non-teaching hospitals (uOR [2.39]; 95% CI, 1.43-3.99), as well as those treated in Level I trauma centers when compared to non-trauma centers (uOR [3.90]; 95% CI, 1.91-7.96).

Fracture Imaging

Among visits with DFF alone, 86.1% [95% CI, 84.9-87.3] had imaging of the wrist performed, with the remainder having fractures identified on forearm imaging (Figure 2). Overall, 40.3% [95% CI, 35.4-42.2] had non-wrist imaging performed. An estimated 37.2% of the APF fractures potentially could have been identified with forearm imaging alone in addition to identifying the DFF as well. That being said, dedicated imaging of the wrist or other anatomical structure may be necessary to better characterize the identified APF on forearm radiographs. Excluding non-forearm imaging, only 18.9% (95% CI, 17.4-20.3) had non-wrist/non-forearm imaging. Dedicated imaging of the humerus or elbow occurred less frequently at 1.4% (95% CI, 1.2-1.5), and 8.1% (95% CI, 6.9-9.2), respectively.

There were differences in the cases with non-standard imaging (imaging at locations other than the wrist or forearm) performed by demographic- and facility-level characteristics (Table 3). Among those with DFF only, the odds of non-standard imaging were approximately two times greater among those ≥18 years of age compared to those <18 years. Additional imaging occurred more frequently among females (uOR [1.09]; 95% CI, 1.01-1.17). Compared to those with private insurance, additional imaging that was non-standard occurred most frequently among

Table 2. Characteristics of population with associated proximal fractures among those with distal forearm fractures, National Emergency Department Sample 2013.

Patient or Facility Characteristics	DFF only (weighted n =292,919)		APF among those with DFF (weighted n =4,836)		uOR (95% CI)
	Weighted N	% (95% CI)	Weighted N	% (95% CI)	
Patient characteristics					
Age (years)					
< 18	129,328	48.3 (40.0-56.6)	2,337	44.2 (42.2-46.1)	*Ref*
18-44	41,037	17.4 (14.6-20.2)	842	14.0 (13.3-14.7)	1.14 (0.84-1.53)
45-64	61,568	20.8 (16.8-24.8)	1,005	20.8 (16.8-24.8)	0.90 (0.65-1.26)
≥65	60,986	13.5 (10.3-16.7)	652	13.5 (10.3-16.7)	0.59 (0.41-0.86)
Sex					
Male	130,242	44.5 (43.6-45.3)	2,475	51.2 (46.7-55.6)	*Ref*
Female	162,663	55.5 (54.7-56.4)	2,360	48.8 (44.4-53.3)	0.76 (0.64-0.91)
Payer					
Medicare	59,331	20.3 (19.3-21.3)	758	15.7 (12.1-19.2)	0.71 (0.53-0.96)
Medicaid	65,458	22.4 (21.0-23.8)	1,144	23.7 (20.5-26.9)	0.97 (0.82-1.14)
Self-pay	28,889	9.9 (9.1-10.6)	442	9.2 (7.2-11.1)	0.85 (0.65-1.11)
No charge	1,572	0.5 (0.3-0.7)	33	0.7 (0.2-1.2)	1.16 (0.63-2.13)
Other	16,776	5.7 (5.1-6.3)	283	5.9 (4.1-7.6)	0.94 (0.66-1.34)
Private (including HMO)	120,451	41.2 (39.6-42.8)	2,168	44.9 (40.2-49.6)	*Ref*
Patient residence rurality					
Large central metropolitan	68,597	23.7 (20.2-27.1)	1,617	33.8 (24.3-43.2)	*Ref*
Large fringe metropolitan	79,726	27.5 (24.1-30.9)	1,217	25.4 (20.5-30.3)	0.65 (0.47-0.90)
Medium metropolitan	57,314	19.8 (16.6-22.9)	713	14.9 (9.1-20.6)	0.53 (0.31-0.91)
Small metropolitan	21,925	7.6 (5.7-9.4)	321	6.7 (3.3-10.1)	0.62 (0.33-1.18)
Micropolitan	37,476	12.9 (11.4-14.4)	588	12.3 (8.3-16.2)	0.67 (0.39-1.13)
Not metropolitan or micropolitan	24,999	8.6 (7.6-9.7)	334	7.0 (4.6-9.3)	0.57 (0.34-0.95)
Facility characteristics					
Hospital urban-rural location					
Large metropolitan	139,148	47.5 (44.0-51.0)	2,870	59.3 (46.3-72.4)	*Ref*
Small metropolitan	73,862	25.2 (22.1-28.3)	1,033	21.4 (12.7-30.0)	0.68 (0.38-1.20)
Micropolitan	36,652	12.5 (10.4-14.6)	479	9.9 (5.6-14.2)	0.63 (0.36-1.11)
Not metropolitan or micropolitan	22,451	7.7 (6.4-9.0)	231	4.8 (2.5-7.0)	0.50 (0.28-0.88)
Collapsed category of small metropolitan and micropolitan	7,451	2.5 (1.1-3.9)	126	2.6 (0.5-4.8)	0.82 (0.42-1.60)
Metropolitan, collapsed category of large and small metropolitan	6,968	2.4 (1.2-3.5)	61	1.3 (0.0-2.8)	0.43 (0.16-1.18)
Non-metropolitan, collapsed category of micropolitan and rural	6,387	2.2 (2.0-2.4)	35	0.7 (0.0-1.8)	0.27 (0.06-1.16)
Hospital Region					
Northeast	64,801	22.1 (19.4-24.8)	822	17.0 (8.6-25.4)	1.14 (0.69-1.90)
Midwest	55,551	19.0 (16.5-21.5)	1,348	27.9 (12.4-43.4)	2.19 (1.07-4.47)
South	125,913	43.0 (39.5-46.5)	2,148	44.4 (28.9-59.9)	1.54 (0.91-2.60)
West	46,655	15.9 (13.0-18.9)	518	10.7 (6.0-15.4)	*Ref*

Table 2. Continued.

Patient or facility characteristics	DFF only (weighted n =292,919)		APF among those with DFF (weighted n =4,836)		uOR (95% CI)
	Weighted N	% (95% CI)	Weighted N	% (95% CI)	
Hospital control/ownership of hospital					
Government or private, collapsed category	179,975	61.4 (58.2-64.7)	3,516	72.7 (63.8-81.7)	1.57 (0.87-2.83)
Government, nonfederal, public	24,387	8.3 (6.5-10.2)	278	5.8 (3.1-8.5)	0.92 (0.56-1.51)
Private, non-profit, voluntary	51,415	17.6 (14.9-20.2)	601	12.4 (7.7-17.2)	0.94 (0.58-1.52)
Private, investor-own	25,610	8.7 (7.4-10.1)	296	6.1 (3.4-8.8)	0.93 (0.55-1.57)
Private, collapsed category	11,532	3.9 (2.9-4.9)	144	3.0 (1.2-4.7)	*Ref*
Teaching status of hospital					
Metropolitan non-teaching	117,708	40.2 (36.9-43.5)	1,267	26.2 (17.7-34.7)	*Ref*
Metropolitan teaching	109,721	37.5 (33.7-41.2)	2,823	58.4 (45.4-71.4)	2.39 (1.43-3.99)
Non-metropolitan hospital	65,491	22.4 (19.9-24.8)	745	15.4 (9.7-21.2)	1.06 (0.82-1.36)
Hospital trauma center level					
Non-trauma center	127,799	43.6 (40.2-47.1)	1,528	31.6 (20.8-42.4)	*Ref*
Trauma Level I	42,066	14.4 (11.2-17.5)	1,958	40.5 (22.7-58.3)	3.90 (1.91-7.96)
Trauma Level II	24,860	8.5 (6.1-10.9)	311	6.4 (3.0-9.8)	1.05 (0.69-1.59)
Trauma Level III	25,452	8.7 (6.7-10.7)	258	5.3 (2.5-8.2)	0.85 (0.56-1.29)
Non-trauma or trauma Level III	59,249	20.2 (17.9-22.6)	598	12.4 (7.8-16.9)	0.84 (0.63-1.13)
Trauma Level 1 or II, collapsed	13,492	4.6 (3.6-5.6)	184	3.8 (1.4-6.2)	1.14 (0.61-2.11)

DFF, distal forearm fracture; *APF,* associated proximal fracture; *uOr*, unadjusted odds ratio; *CI*, confidence interval; *HMO,* health maintenance organization.

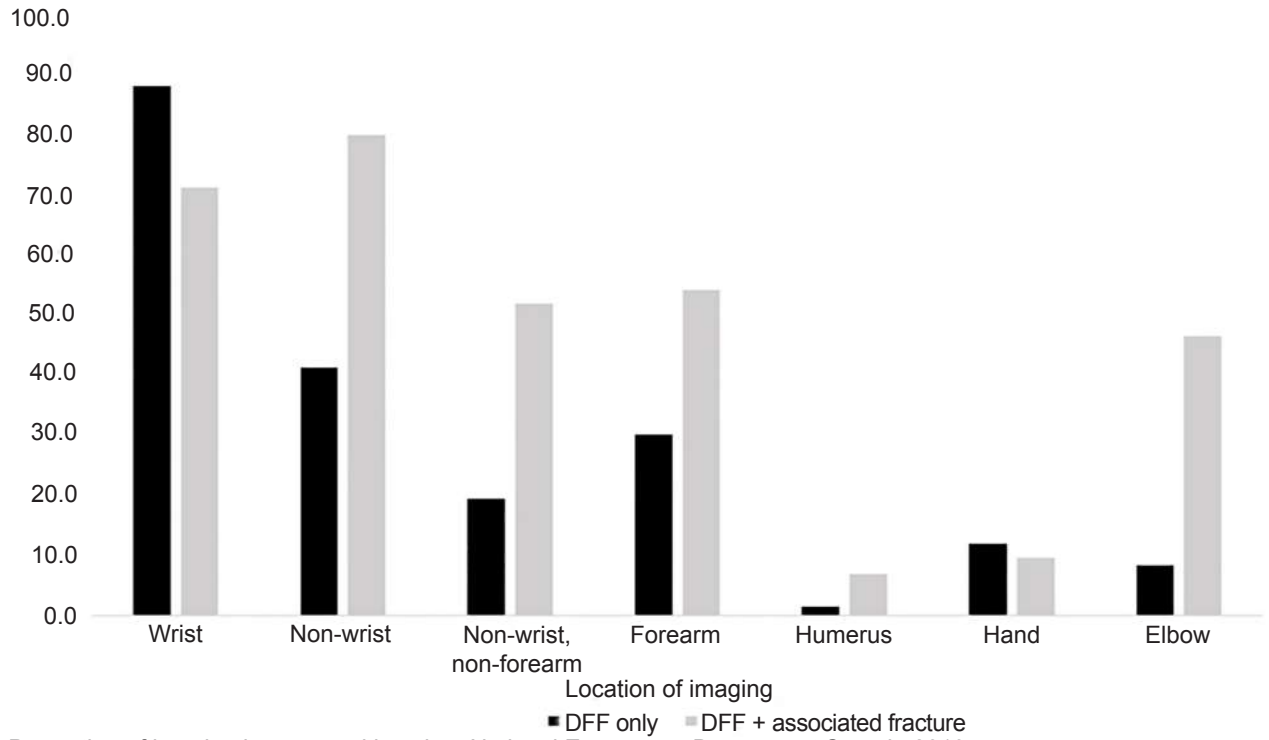

Figure 2. Proportion of imaging by type and location, National Emergency Department Sample 2013.

Table 3. Distribution of associated proximal fractures among those with distal forearm fractures.

APF codes	Name	Weighted N	%	Cumulative %
813.21	Fracture shaft, radius	1,673	15.20	15.20
813.05	Fracture radius head, closed	1,639	14.89	30.09
812.41	Supracondylar fracture humerus, closed	1,428	12.97	43.06
813.83	Closed fracture of unspecified part of radius and ulna	839	7.62	50.68
813.01	Fx olecranon proc ulna, closed	720	6.54	57.22
813.22	Fracture of shaft ulna	716	6.50	63.73
813.81	Closed fracture of unspecified part of radius	710	6.45	70.18
813.23	Fracture of radius and ulna, closed	703	6.39	76.56
813.82	Closed fracture of unspecified part of ulna	344	3.13	79.69
813.33	Fracture of radius and ulna, open	239	2.17	81.86
812.42	Fx humerus, lateral condyle, closed	230	2.09	83.95
813.02	Fx coronoid proc ulna, closed	223	2.03	85.97
813.07	Fx upper radius Nec/Nos, closed	215	1.95	87.93
813.04	Fx upper ulna Nec/Nos, closed	212	1.93	89.85
812.43	Fx humerus, medial condyle, closed	129	1.17	91.02
813.32	Fracture of shaft of ulna, open	125	1.14	92.16
812.31	Fracture of humerus shaft, open	110	1.00	93.16
813.11	Fracture of humerus shaft, open	103	0.94	94.10
812.44	Closed fracture of unspecified condyle of humerus	94	0.85	94.95
813.31	Open fracture of shaft of radius	89	0.81	95.76
812.49	Other closed fracture of lower end of radius	87	0.79	96.55
812.51	Open supracondylar fracture of humerus	85	0.77	97.32
813.15	Open fracture of head of radius	44	0.40	97.72
813.93	Open fracture of unspecified part of radius and ulna	43	0.39	98.11
812.53	Open fracture of medial condyle of humerus	36	0.33	98.44
813.18	Fracture of radius with ulna upper end open	29	0.26	98.70
813.13	Open Monteggia's fracture	25	0.23	98.93
812.52	Open fracture of lateral condyle of humerus	23	0.21	99.14
813.92	Open fracture of unspecified part of ulna	22	0.20	99.34
813.91	Open fracture of coronoid process of radius	22	0.20	99.54
813.12	Open fracture of coronoid process of ulna	20	0.18	99.72
812.54	Open fracture of unspecified condyle of humerus	18	0.16	99.88
813.14	Other and unspecified open fractures of proximal end of ulna	10	0.09	99.97
812.59	Open fracture of lower end of humerus	3	0.03	100.00

Dx, diagnosis; *Fx*, fracture; *Nec/Nos*, not elsewhere classified/not otherwise specified.

Table 4. Factors associated with non-standard imaging of patients with distal forearm fractures, National Emergency Department Sample, 2013.

Patient or facility characteristics	Non-standard imaging (n =55,236)		Standard imaging (n =237,683)		uOR* (95% CI)	aOR** (95% CI)
	Weighted N	% (95% CI)	Weighted N	% (95% CI)		
Patient characteristics						
Age (years)						
< 18	17,252	31.2 (28.2-34.3)	112,077	47.2 (45.2-49.1)	*Ref*	*Ref*
18-44	10,081	18.2 (17.0-19.5)	30,957	13.0 (12.3-13.8)	2.12 (1.84-2.43)	2.29 (2.01-2.62)
45-64	13,993	25.3 (23.9-26.7)	47,574	20.0 (19.2-20.9)	1.91 (1.67-2.18)	2.21 (1.94-2.51)
≥65	13,911	25.2 (23.6-26.7)	47,075	19.8 (18.8-20.8)	1.92 (1.67-2.21)	2.17 (1.87-2.51)
Sex						
Male	23,637	42.8 (41.0-44.6)	106,605	44.9 (44.0-45.8)	*Ref*	*Ref*
Female	31,599	57.2 (55.4-59.0)	131,064	55.1 (54.2-56.0)	1.09 (1.01-1.17)	0.88 (0.83-0.93)
Payer						
Medicare	13,747	24.9 (23.2-26.7)	45,584	19.2 (18.2-20.2)	1.54 (1.38-1.73)	1.22 (1.11-1.34)
Medicaid	11,311	20.5 (19.1-22.0)	54,148	22.8 (21.3-24.3)	1.07 (0.97-1.18)	1.23 (1.12-1.35)
Self-pay	6,609	12.0 (10.3-13.7)	22,279	9.4 (8.8-10.0)	1.52 (1.29-1.78)	1.23 (1.11-1.36)
No charge	416	0.8 (0.4-1.1)	1,157	0.5 (0.3-0.7)	1.84 (1.20-2.81)	1.14 (0.82-1.58)
Other	3,338	6.1 (5.3-6.8)	13,438	5.7 (5.0-6.3)	1.27 (1.11-1.46)	1.06 (0.95-1.19)
Private (Including HMO)	19,721	35.8 (33.3-38.2)	100,730	42.4 (40.8-44.1)	*Ref*	*Ref*
Patient residence rurality						
Large central metropolitan	16,134	29.5 (24.9-34.1)	52,463	22.3 (18.8-25.8)	*Ref*	*Ref*
Large fringe metropolitan	14,479	26.4 (22.4-30.4)	65,248	27.7 (24.3-31.2)	0.72 (0.61-0.86)	0.88 (0.72-1.08)
Medium metropolitan	11,102	20.3 (14.4-26.1)	46,211	19.6 (16.7-22.6)	0.78 (0.55-1.11)	0.94 (0.66-1.36)
Small metropolitan	3,371	6.2 (4.5-7.8)	18,553	7.9 (5.9-9.8)	0.59 (0.47-0.74)	0.76 (0.60-0.98)
Micropolitan	5,683	10.4 (8.6-12.1)	31,792	13.5 (11.9-15.1)	0.58 (0.48-0.71)	1.10 (0.87-1.39)
Not metropolitan or micropolitan	4,002	7.3 (6.0-8.6)	20,997	8.9 (7.8-10.0)	0.62 (0.51-0.75)	1.10 (0.86-1.41)
Family characteristics						
Hospital urban-rural location						
Large Metropolitan	30,140	54.6 (49.3-59.8)	109,008	45.9 (42.2-49.6)	*Ref*	
Small Metropolitan	13,736	24.9 (19.0-30.7)	60,125	25.3 (22.2-28.4)	0.83 (0.61-1.12)	
Micropolitan	4,880	8.8 (7.2-10.5)	31,773	13.4 (11.0-15.7)	0.56 (0.46-0.67)	
Not metropolitan or micropolitan	3,287	6.0 (4.7-7.2)	19,164	8.1 (6.7-9.5)	0.62 (0.51-0.75)	
Collapsed category of small metropolitan and micropolitan	1,223	2.2 (0.9-3.5)	6,228	2.6 (1.2-4.1)	0.71 (0.61-0.83)	
Metropolitan, collapsed category of large and small metropolitan	1,201	2.2 (0.9-3.4)	5,767	2.4 (1.2-3.6)	0.75 (0.56-1.01)	

Table 4. Continued.

Patient or facility characteristics	Non-standard imaging (n =55,236)		Standard imaging (n =237,683)		uOR* (95% CI)	aOR** (95% CI)
	Weighted N	% (95% CI)	Weighted N	% (95% CI)		
Patient characteristics						
Hospital urban-rural location						
Non-metropolitan, collapsed category of micropolitan and rural	770	1.4 (0.5-2.3)	5,617	2.4 (2.0-2.7)	0.50 (0.22-1.12)	
Hospital region						
Northeast	14,990	27.1 (21.7-32.6)	49,811	20.9 (18.3-23.6)	1.65 (1.12-2.41)	1.47 (0.91-2.39)
Midwest	8,633	15.6 (12.5-18.7)	46,918	19.7 (17.1-22.4)	1.01 (0.73-1.39)	0.99 (0.70-1.41)
South	24,396	44.2 (39.2-49.1)	101,517	42.7 (39.1-46.3)	1.31 (0.98-1.77)	1.22 (0.89-1.69)
West	7,217	13.1 (9.5-16.6)	39,438	16.6 (13.4-19.8)	*Ref*	*Ref*
Hospital control/ ownership of hospital						
Government or private, collapsed category	37,579	68.0 (64.2-71.9)	142,395	59.9 (56.5-63.4)	1.74 (1.40-2.15)	0.82 (0.57-1.19)
Government, nonfederal, public	3,196	5.8 (4.6-7.0)	21,191	8.9 (6.8-11.1)	0.99 (0.75-1.32)	0.79 (0.57-1.09)
Private, non-profit, voluntary	8,823	16.0 (13.1-18.9)	42,592	17.9 (15.2-20.6)	1.36 (1.12-1.67)	0.97 (0.73-1.30)
Private, investor-owned	4,118	7.5 (6.1-8.8)	21,492	9.0 (7.6-10.5)	1.26 (1.04-1.53)	0.86 (0.63-1.18)
Private, collapsed category	1,520	2.8 (1.9-3.6)	10,012	4.2 (3.1-5.3)	*Ref*	*Ref*
Teaching status of hospital						
Metropolitan non-teaching	19,049	34.5 (30.4-38.6)	98,658	41.5 (38.0-45.0)	*Ref*	*Ref*
Metropolitan teaching	27,251	49.3 (44.1-54.5)	82,470	34.7 (30.8-38.6)	1.71 (1.39-2.11)	1.24 (0.98-1.57)
Non-metropolitan hospital	8,937	16.2 (13.8-18.6)	56,554	23.8 (21.1-26.5)	0.82 (0.71-0.94)	0.74 (0.61-0.89)
Hospital trauma center level						
Non-trauma center	21,996	39.8 (35.2-44.4)	105,803	44.5 (40.9-48.1)	*Ref*	*Ref*
Trauma Level I	14,069	25.5 (19.2-31.8)	27,997	11.8 (8.6-15.0)	2.42 (1.62-3.61)	2.28 (1.48-3.51)
Trauma Level II	4,636	8.4 (5.6-11.1)	20,225	8.5 (6.1-10.9)	1.10 (0.91-1.33)	1.09 (0.86-1.38)
Trauma Level III	3,047	5.5 (3.7-7.3)	22,405	9.4 (7.3-11.6)	0.65 (0.50-0.85)	0.74 (0.57-0.95)
Non-trauma or trauma Level I	9,623	17.4 (14.8-20.1)	49,626	20.9 (18.4-23.4)	0.93 (0.81-1.08)	1.00 (0.85-1.19)
Trauma Level I or II, collapsed	1,865	3.4 (2.5-4.2)	11,627	4.9 (3.8-6.0)	0.77 (0.60-0.99)	1.00 (0.74-1.37)

CI, confidence interval; *uOR*, unadjusted odds ratio; *aOR*, adjusted odds ratio; *HMO*, health maintenance organization.
*Represents the odds of receiving non-standard imaging (non-wrist or forearm by each characteristic.
**Adjusted for all demographic and facility variables listed, except Hospital urban-rural location, due to collinearity.

no-charge visits (visits for which there is no fee charged generally for charity, special research, or teaching)[16] or self-pay (uOR [1.84]; 95% CI, 1.20-2.81), those with Medicare (OR [1.54]; 95% CI, 1.38-1.73), and self-pay visits (uOR [1.52]; 95% CI, 1.29-1.78). Compared to non-trauma centers, the odds of non-standard imaging in Level 1 trauma centers were 2.42 (95% CI, 1.62–3.61) times greater. Model estimates from the sensitivity analysis were similar across all three definitions of DFF used (Supplemental File).

Multivariable Analysis

Among patient-level factors in the final multivariable model, age, sex, and payer were still independently associated with non-standard imaging. Compared to metropolitan non-teaching facilities, the unadjusted odds of non-standard imaging were 1.28 (95% CI, 1.02-1.62) and 0.73 (95% CI, 0.61-0.87) among metropolitan teaching facilities and non-metropolitan hospitals, respectively. This suggests patients presenting to teaching hospitals receive more radiographs than those at rural hospitals. The unadjusted odds of non-standard imaging was 2.16 (95% CI, 1.41-3.30) among Level 1 trauma centers compared to non-trauma centers.

Cost Analysis

If every DFF presenting to the ED received a radiograph (assumed to be a three-view elbow radiograph) to evaluate for APF, it would cost $21.2 million yearly and $4,455 at $71 per radiograph per APF identified. In our sample, 8.1% of those with DFF received this radiograph series costing $1.7 million. Using Medicare reimbursement as a proxy for health system cost, $3.95 million is spent annually for additional imaging of DFF who do not have APF. In sensitivity analyses varying the cost of a radiograph (to account for potential underestimation of the true cost of imaging using the Medicare reimbursement rate), the cost of identifying an APF through imaging of all DFF patients ranged from $3,341 to $6,683.

DISCUSSION

We report a low incidence (1.6%) of APF associated with the diagnosis of DFF. The low incidence of APF is likely a significant reason the previous literature on APF has been limited to case reports.[12,17-29] In our series, the most common APFs were radial shaft fractures (15.2%), followed by radial head fractures (14.9%), and supracondylar humerus fractures (12.9%) (Table 3). Forty percent of patients with an APF had fractures that could have been identified on elbow radiographs. Nearly half (45%) of those with an APF had elbow radiographs performed (Table 4). Although this fracture rate is 5% lower than the percentage of patients who had an APF and received an elbow radiograph, this may be an acceptable rate of potential imaging. However, combined with the 8.1% of those without an APF who received radiographs of the elbow, this may be an area where particular attention should be paid to the physical examination in identifying patients who are at risk for osseous injury.

The use of the physical examination to identify patients at very low risk for fractures of the knee and ankle has been used to reduce low-value imaging.[30,31] That being said, the use of physical examination to accurately assess who is at risk for osseous injury at the elbow has had mixed results.[32-34] The East Riding Elbow Rule, which combines elbow extension, osseous tenderness, and bruising, boasted 100% sensitivity for elbow fracture and would decrease elbow radiographs by an estimated 15%.[31] Subsequently, studies using similar methodology have not had as promising results in accurately identifying those at risk of elbow fracture through the use of physical exam; sensitivities for elbow extension alone ranged from 73-88% with the combination of elbow extension and osseous tenderness having sensitivities from 96-98%.[32,33]

It is unclear whether routine imaging of the elbow is necessary or cost effective in those with DFF. However, the routine practice of obtaining imaging of the joint proximal to the known fracture site has been evaluated in patients with ankle fractures with nearly 64% of those patients receiving adjacent joint imaging and only 9.9% of patients having an APF, although it is unclear how these results would translate to the upper extremity.[35]

Demographic considerations may also play a role in the need for additional imaging. The higher proportion of APFs in trauma centers is noteworthy, because it suggests that either 1) increased imaging identifies fractures that are missed in non-trauma centers; or (2) the patient population in trauma centers is different from those in non-trauma centers. Patients being treated at Level 1 trauma centers were 2.42 times more likely (95% CI, 1.62-3.61) to undergo imaging of the non-wrist or non-forearm in patients without an APF. They may also be more likely to have sustained a more significant mechanism of injury necessitating additional imaging. Furthermore, trainees at these institutions initially evaluate patients, and prior reports have associated junior trainees with increased diagnostic testing. Additionally, patients who receive care at academic institutions have a higher level of testing performed.[36] These findings have been consistent across a variety of hospital settings including EDs, intensive care units, general internal medicine wards, and units treating ischemic strokes.[36-39]

Our analysis also showed that imaging of the non-wrist and non-forearm occurred more frequently among females who only had a DFF (unadjusted odds ratio [1.09]; 95% CI, 1.01-1.17). This could be related to previous work revealing that DFF is more common in females.[2] However, females were less likely to have an APF in our study.

LIMITATIONS

Our study has several limitations. First, our analysis was done retrospectively using the NEDS database to obtain a large, diverse, and generalizable data sample. However, there are several inherent limitations to a retrospective database analysis. The NEDS database is a collection of claims data, not medical

records. This may be relevant given that only 64% of patients diagnosed with DFF had complete data in the NEDS database. We limited our analysis to records from all those with DFF who had recorded imaging in the database. Accordingly, all patients without imaging were eliminated from our analysis since the diagnosis of DFF was contingent upon imaging.

Second, when defining our cohort we used increasingly stricter ICD-9 definitions and ultimately ran an analysis on the strictest definition to minimize uncertainty regarding the precise anatomic location of the DFF. This may have excluded some DFFs that were coded using general codes, which could lead to an underestimate of concomitant fractures. We intentionally used this strategy to define an upper limit for the actual estimate, because the rate of APF in reality may be lower than the 1.6% we report. However, model estimates from our sensitivity analysis were similar across all three definitions of DFF, suggesting the APF rate of 1.6% may be accurate.

Third, our cohort was limited to patients who were discharged from the ED. One could argue patients admitted after sustaining a DFF were more likely to experience more significant trauma, which could put those patients at higher risk for APF.

Fourth, in our analysis APFs were seen more often in teaching hospitals. In this setting more radiographs were also performed. With that said, even those without APFs were more likely to receive non-standard imaging in teaching hospitals when compared to non-teaching hospitals (Table 4). One could contend that the direct correlation between the increased testing and the greater rate of APF identified justifies performing additional testing in all patients with DFF. We assert that there are other potential means to identify those at risk for APF in a more practical and cost-efficient manner (eg, the physical examination). However, this study cannot address which radiographs were clinically indicated.

Lastly, we assume that all APFs were identified. We were unable to determine whether a patient was subsequently diagnosed with an associated proximal fracture that was missed during the ED visit.

CONCLUSION

In patients with a DFF, the incidence of having an APF is low. Further study to identify risk factors for APF based on mechanism of injury, physical examination, and demographic factors may result in identifying patients at variable degrees of risk for APF.

ACKNOWLEDGMENTS

This research was supported by the University of Iowa College of Medicine, the Department of Emergency Medicine, and in part through computational resources provided by the University of Iowa, Iowa City, Iowa.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Clinical Features and Outcomes Associated with Angioedema in the Emergency Department

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Section Editor: David Thompson, MD
Submission history: Submitted February 25, 2019; Revision received June 27, 2019; Accepted June 26, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.6.42852

Introduction: Angioedema represents self-limited, localized swelling of submucosal or subcutaneous tissues. While the underlying etiology may be undeterminable in the emergent setting, nonhistaminergic and histaminergic angioedema respond differently to therapeutic interventions, with implications for empiric treatment. Clinical features and outcome differences among nonhistaminergic vs histaminergic angioedema patients in the emergency department (ED) are poorly characterized. We aim to describe the clinical characteristics and outcomes among ED patients with angioedema by suspected etiology.

Methods: This was a 10-year retrospective study of adult ED patients with angioedema, using data abstracted from the electronic health record. We evaluated univariable associations of select clinical features with etiology and used them to develop a multivariable logistic regression model for nonhistaminergic vs histaminergic angioedema.

Results: Among 450 adult angioedema patients, the mean +/- standard deviation age was 57 +/- 18 years, and 264 (59%) were female. Among patients, 30% had suspected nonhistaminergic angioedema, 30% had suspected histaminergic angioedema, and 40% were of unknown etiology. As compared to histaminergic angioedema, nonhistaminergic angioedema was associated with angiotensin-converting enzyme inhibitors (ACEI) or use of angiotensin II receptor blockers (ARB) (odds ratio [OR] [60.9]; 95% confidence interval [CI], 23.16-160.14) and time of onset one hour or more prior to ED arrival (OR [5.91]; 95% CI,1.87-18.70) and was inversely associated with urticaria (OR [0.05]; 95% CI, 0.02-0.15), dyspnea (OR [0.23]; 95% CI, 0.08-0.67), and periorbital or lip edema (OR [0.25]; 95% CI, 0.08-0.79 and OR [0.32]; 95% CI, 0.13-0.79, respectively).

Conclusion: As compared to histaminergic angioedema, patients with nonhistaminergic angioedema were more likely to present one hour or more after symptom onset and take ACEI or ARB medications, and were less likely to have urticaria, dyspnea, or periorbital or lip angioedema. Identification of characteristics associated with the etiology of angioedema may assist providers in more rapidly initiating targeted therapies. [West J Emerg Med. 2019;20(5)760-769.]

INTRODUCTION

Angioedema is a self-limited and localized swelling of the submucosal or subcutaneous tissues. This process is caused by a temporary increase in vascular permeability allowing passage of fluid from the intravascular space to the interstitial space, and is mediated through the actions of vasoactive substances, primarily histamine or bradykinin.[1] Angioedema is non-pitting and is not gravity dependent, and can involve myriad physical locations, including anatomic structures of the upper airway.[2,3] While rare, death due to asphyxiation has been described, and concern about airway compromise is frequently the primary determinant of the initial management and disposition of patients presenting with angioedema to the emergency department (ED).[4-7] Among patients presenting to the ED with angioedema, approximately one-third are associated with angiotensin-converting enzyme inhibitors (ACEI), representing the most common bradykinin-mediated angioedema syndrome encountered in this setting.[8,9] The remainder are comprised of histamine-mediated syndromes and, to a far lesser extent, hereditary and acquired angioedema syndromes related to complement aberrations.[3,8-12] Angioedema of unknown etiology has represented a large percentage (30-59%) of cases in previously reported cohorts.[3,13-15]

Histaminergic angioedema arises from mast cell degranulation and is effectively treated with epinephrine, antihistamines, and corticosteroids.[16] Epinephrine is the first-line therapy for life-threatening histaminergic and undifferentiated angioedema.[16] The etiologies of bradykinin-mediated angioedema include hereditary angioedema syndromes (HAE), acquired catabolism of C1 inhibitor (C1-INH), and ACEI-associated angioedema.[16-19] Targeted interventions for acute presentations of hereditary or acquired angioedema due to C1-INH deficiency include C1-INH concentrates (Berinert P; CSL Behring, Marburg, Germany), bradykinin-receptor antagonists (icatibant; Jerini, Berlin, Germany), or plasma kallikrein inhibitors (ecallantide; Dyax Corp, Cambridge, Massachusetts).[1,20] The care of ACEI-associated angioedema in the emergent setting includes acute airway management and discontinuation of the offending medication.[7,16] While initial results among patients receiving icatibant for ACEI-associated angioedema were promising, larger trials evaluating targeted HAE therapies for ACEI-associated angioedema have yielded disappointing results.[17,21-23]

Laboratory studies are of limited utility in the emergent setting. A normal C4 level in the acute setting reasonably excludes HAE type I and type II, and an elevated tryptase level supports a histaminergic etiology.[1] However, these studies may not be available in some settings, and even if they were, results would not be available in a timeframe sufficient to guide ED care.[16,24] However, the suspected etiology of angioedema does have pragmatic implications in the ED, where critical decisions regarding empiric therapy, airway management, and patient disposition must be rapidly made.

Population Health Research Capsule

What do we already know about this issue?
Angioedema arises from histamine or bradykinin effect, and the underlying etiology determines response to therapeutic interventions.

What was the research question?
Are there clinical features that differentiate ED patients with histaminergic versus nonhistaminergic angioedema?

What was the major finding of the study?
Patients with nonhistaminergic angioedema are less likely to present with urticaria, dyspnea, or periorbital or lip edema.

How does this improve population health?
Identification of clinical characteristics associated with histaminergic or nonhistaminergic angioedema syndromes may guide emergency providers in initiating treatment.

Given the differences in pathophysiology and response to targeted therapies of the various angioedema clinical syndromes and the absence of timely laboratory studies that can help differentiate the underlying etiology, an understanding of the differences in clinical features among histaminergic vs nonhistaminergic angioedema may assist the emergency provider in determining the underlying etiology. However, differences in clinical features among histaminergic vs nonhistaminergic angioedema syndromes are not well described. We aimed to describe the clinical features, management, and outcomes of a 10-year cohort of patients who presented with angioedema to a large quaternary ED, identifying clinical factors and outcomes associated with angioedema etiology.

METHODS

Study Design, Setting and Participants

Our retrospective cohort study was approved by the Mayo Clinic Institutional Review Board. All adult patients (age ≥ 18 years) evaluated for angioedema in the ED of Mayo Clinic Hospital (Rochester, Minnesota) from January 1, 2005, to December 31, 2014, were eligible for inclusion. The number of cases during the study period determined the study size. The ED at our quaternary care academic institution had an average annual census of 74,000 during the study period.

Patients were identified by diagnostic codes for angioedema (*International Classification of Diseases, Ninth Revision [*ICD-9*]* code 995.1), hereditary angioedema (*ICD-9* 277.6), edema of the pharynx or nasopharynx (ICD-9 478.25), or edema of the larynx (ICD-9 478.6). ICD-9 diagnostic codes for anaphylaxis were not used to identify patients; however, patients identified with angioedema and associated anaphylaxis were included. We obtained and reviewed charts of patients with angioedema identified within three days from an ED evaluation. Patients with subjective angioedema (ie, no documented swelling) and angioedema that had resolved prior to ED arrival were excluded. We also excluded patients with swelling caused by another identifiable etiology, such as lymphedema, localized infection, trauma, or inflammatory response from irritant substance. All patients evaluated at our institution were asked for permission to use their medical records for research; those who declined were excluded. Our study adheres to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines for reporting observational studies.[25]

Data Sources and Measurement

We abstracted data from the electronic health record (EHR) using a standardized chart review process.[26] All ED visits were independently extracted in duplicate by an undergraduate student (K.A.G.) and a medical student (L.O.J.S.). Students were trained by the principal investigator (PI) (B.J.S) on 20 random charts, and coding rules were developed. Investigators met biweekly to discuss inconsistencies or ambiguities with the PI, and these charts were again reviewed in detail to ensure accuracy of coding. We developed additional abstraction instructions as needed to ensure consistent and accurate data. A sample of 75 visits (10.0%) was independently extracted by the PI, and inter-rater reliability with the final data extracted by the students was calculated for key variables using the Cohen's kappa statistic. Key variables included the following: time of onset; urticaria; airway intervention; disposition; etiology of angioedema in ED; etiology of angioedema at allergy-immunology consultation; and 30-day mortality. Interobserver agreement (kappa) was strong for most variables, and ranged from 0.70 to 1.0.

We collected and managed study data using REDCap (Research Electronic Data Capture, Nashville, TN) electronic data capture tools hosted at Mayo Clinic.[27]

Variables and outcomes

We defined angioedema as localized subcutaneous or submucosal swelling objectively described by the provider documentation in the EHR. Swelling was required to be present on physical examination documentation. When notes were ambiguous among providers, the documentation of the attending physician was given preference. We classified angioedema into three categories: nonhistaminergic angioedema, histaminergic angioedema, and angioedema of unknown etiology. This classification was determined based on documentation of the suspected cause of angioedema reported by the ED provider, dismissing hospital physician, or allergist-immunologist documentation, when available. The final suspected etiology was based on the allergist-immunologist documentation and diagnosis if the patient had allergist-immunologist evaluation, the hospital dismissal diagnosis if the patient was admitted to the hospital, or the ED provider diagnosis if the patient was not admitted and did not have allergist-immunologist evaluation.

Nonhistaminergic angioedema included ACEI-associated angioedema, HAE type I and type II, acquired angioedema with C1-INH deficiency, and HAE with normal C1-INH. Histaminergic angioedema included patients presenting with angioedema and a temporally-related exposure to a likely allergen (ie, medications, foods, and stinging insects) with rapid development of symptoms, and angioedema with multisystem involvement and documented anaphylaxis. Angioedema was categorized as unknown etiology when clear provider documentation of unknown etiology existed, when no clear etiologic agent could be identified on review of the documentation, and when features or inciting causes of both histaminergic and nonhistaminergic syndromes were documented by the provider and were unable to be reconciled.

We reviewed pertinent documentation from the ED evaluation, prehospital and referring hospital, when applicable, and hospital course, as were any allergy-immunology consultation records. We collected 1) baseline characteristics: demographic information, medical history, medications and allergies; 2) history and physical exam: suspected triggers of angioedema, time of onset relative to ED presentation, location of angioedema, clinical signs and symptoms associated with angioedema; 3) suspected cause of angioedema by the emergency provider; 4) treatment provided in the ED; 5) airway management; 6) ED disposition; 7) suspected cause of angioedema at hospital discharge; 8) hospital length of stay, in-hospital mortality and 30-day mortality; 9) allergy-immunology evaluation (either during an associated hospitalization or within 30 days of the index ED visit) and suspected cause of the angioedema by an allergist-immunologist, when available. We categorized the palate, uvula, and tonsillar pillars as pharyngeal structures and the epiglottis, arytenoids, aryepiglottic folds, false vocal cords and true vocal cords as laryngeal structures.

We defined treatment as any medication or blood product used to treat angioedema, including H1 and H2 antihistamine medications, epinephrine, corticosteroids, albuterol, fresh frozen plasma, and targeted therapies such as C1-INH concentrates, bradykinin-receptor antagonists, or kallikrein inhibitors. The need for tracheal intubation was defined as a tracheal intubation attempt. Fiberoptic laryngoscopies with a bronchoscope prepared for intubation were not categorized as a tracheal intubation attempt unless an attempt to intubate the trachea was

documented. ED disposition included home, ED observation, hospital admission (including hospital observation admission), intensive care unit (ICU) admission, and death in the ED. Disposition following ED observation status was collected. In-hospital and 30-day mortality included deaths for all causes.

Statistical Methods

We summarized continuous variables with means and standard deviations (SD). Categorical features were summarized with frequency counts and percentages. Comparisons of features by etiology were evaluated using analysis of variance, Kruskal-Wallis, chi-square, and Fisher's exact tests. We further evaluated associations of select features with type of etiology (histaminergic vs nonhistaminergic) using logistic regression models and summarized them with odds ratios (OR) and 95% confidence intervals (CI). Age was analyzed as a continuous variable. The OR represents the odds of nonhistaminergic angioedema for each 10-year increase in age (Table 3). Multivariable models were developed using forward selection. We performed statistical analyses using SAS version 9.4 (SAS Institute; Cary, NC). All tests were two-sided, and p-values <0.05 were considered statistically significant.

RESULTS

Participants

We identified 752 ED visits potentially eligible for our study, of which 450 visits among 400 distinct patients met our inclusion criteria and were available for analysis. We excluded visits with presentations attributable to an infectious etiology (32); isolated urticaria (25); complications of a malignancy or mass (23); a traumatic, burn-related, or caustic etiology (13); subjective angioedema (13); post-procedural swelling (6); anaphylaxis without angioedema (3); lymphedema (1); or internal jugular vein thrombosis (1). We excluded visits if the patient left prior to evaluation (4) or had angioedema in the prehospital setting that had resolved upon ED evaluation (15). Three patients who declined research authorization were excluded. The remaining 163 excluded ED visits were unrelated to angioedema, and were captured in the ICD-9 diagnostic code query due to a prior angioedema diagnosis or subsequent development of angioedema during the hospitalization or a future encounter.

Descriptive Data

The annual rate of angioedema was 0.6 per 1000 ED visits. The mean +/- SD age at presentation was 57 +/- 18 years, and 264 (59%) were female (Table 1). A majority of our cohort was white (89%). African Americans represented 6% of our cohort, and African Americans comprised 4.4% of all patients presenting to our ED during the study period. Eighty-seven (19%) patients were transported by ambulance. Hypertension (61%) was the most common comorbidity, and 45% of patients reported a prior episode of angioedema.

Steroids were the most commonly administered medications (83%) followed by H1 antihistamine medications (79%). Epinephrine was administered in 34% of encounters. Tracheal intubation was required in 33 patients (7%). Patients were frequently discharged to home directly from the ED (38%) or from an ED observation unit (32%). ICU admission occurred in 78 patients (17%). Among the 154 patients who were admitted to an ED observation unit 145 (94%) were discharged, five (3%) were admitted to general care, and four (3%) were admitted to an ICU. A total of 226 (50%) patients had allergy-immunology consultation in the inpatient setting or upon outpatient follow-up. No in-hospital deaths were noted, and mortality within 30 days was rare (1%). No deaths were due to complications of angioedema.

Outcome Data and Main Results

We compared clinical features and outcomes by etiology of angioedema (nonhistaminergic vs histaminergic vs unknown) among all patients in our cohort (Supplemental Appendix). We identified a probable etiology of angioedema in 60% of patient encounters. We found similar frequencies of nonhistaminergic (30%) and histaminergic (30%) angioedema, and in 40% of patients the etiology of angioedema could not be identified. The specific underlying suspected etiology of the angioedema episodes are summarized in Table 2. ACEI-associated angioedema was the most common cause of nonhistaminergic angioedema. Medication hypersensitivity represented the most common cause of histaminergic angioedema.

Table 3 summarizes univariable associations of clinical features and outcomes among the subset of patients with suspected nonhistaminergic vs histaminergic angioedema among our cohort (n=271)**.** Patients presenting with nonhistaminergic angioedema were more likely to be older than those with histaminergic angioedema, more likely to have had symptoms one hour or more prior to ED arrival, and more likely to have tongue or soft palate swelling. ACEI medication use, hypertension, and diabetes were more common among patients diagnosed with nonhistaminergic angioedema. Periorbital angioedema, lip angioedema, and urticaria were less likely among patients with nonhistaminergic angioedema compared to histaminergic.

Patients with nonhistaminergic angioedema were more likely to be admitted to the ICU (OR [2.58]; 95% CI, 1.35-4.93) compared to a non-ICU disposition (home, ED observation and hospital admission) than those with histaminergic angioedema. Those with upper airway involvement, defined as angioedema of the larynx or tongue, were more likely to require ICU admission (OR [11.27]; 95% CI, 5.87-21.63). ICU admission also was more frequent in patients with nonhistaminergic angioedema (OR [2.18]; 95% CI,1.32-3.61) than a combined subset of histaminergic angioedema and angioedema of unknown etiology, an association that remained

Table 1. Features of emergency department (ED) patients presenting with angioedema.

Feature	n=450; n (%)	Feature	n=450; n (%)
Age at visit (Mean ± SD)	56.8 ± 17.9	Shortness of breath	68 (15)
Sex		Abdominal pain	5 (1)
Female	264 (59)	Limb swelling	8 (2)
Race		Syncope	3 (1)
White	398 (89)	Cardiopulmonary arrest	2 (<1)
African-American	25 (6)	Urticaria	117 (26)
All others	25 (6)	Wheezing	29 (6)
Comorbidity (N=449)*		Objective location of angioedema (N=449)*	
Angioedema history	200 (45)	Face	124 (28)
COPD	34 (8)	Periorbital	74 (16)
Asthma	49 (11)	Lips	262 (58)
Hypertension	272 (61)	Uvula	42 (9)
Diabetes	105 (23)	Soft palate	14 (3)
Medications		Pharynx	52 (12)
Neither	255 (57)	Floor of mouth	1 (<1)
ACEI	174 (39)	Tongue	177 (39)
ARB	19 (4)	Larynx	29 (6)
ACEI and ARB	2 (<1)	Neck	8 (2)
ACEI duration (N=167)		Abdomen	5 (1)
<1 month	16 (10)	Genitalia	1 (<1)
1-6 months	12 (7)	Limbs	33 (7)
6-12 months	15 (9)	Treatment*	
>12 months	124 (74)	H1 antihistamine	356(79)
Family history of angioedema (N=269)		H2 antihistamine	230 (51)
Transport by EMS		Epinephrine	153 (34)
Time of onset (N=449)		Corticosteroid	372 (83)
In the ED	8 (2)	Nebulized albuterol	41 (9)
<1 hour	72 (16)	Fresh-frozen plasma	6 (1)
1-6 hours	245 (55)	Berinert © (C1 Esterase Inhibitor [Human])	5 (1)
6-12 hours	56 (12)	Other‡	4(1)
>12 hours	68 (15)	Intubation	33 (7)
Presenting symptoms*		Disposition	
Hoarseness	21 (5)	Home	171 (38)
Voice change	76 (17)	ED observation	145 (32)
Stridor	8 (2)	Hospital admission	56 (12)
Drooling	13 (3)	ICU admission	78 (17)
Facial swelling	4 (1)	Death in hospital	0
Periorbital swelling	74 (16)	Death within 30 days (N=422)	3 (1)
Lip swelling	261 (58)		
Tongue swelling	176 (39)		

*Patient can be included in more than one group.
‡Includes one patient each with blinded study drug, ecallantide, aminocaproic acid, and tranexamic acid, respectively.
COPD, chronic obstructive pulmonary disease; *ACEI,* angiotensin-converting enzyme inhibitor; *ARB,* angiotensin II receptor blockers; *EMS,* emergency medical services; *ED,* emergency department; *ICU,* intensive care unit.

Table 2. Summary of final angioedema etiology, N=450.

Final angioedema etiology	n (%)
Nonhistaminergic angioedema	136 (30)
ACEI-associated	118 (26)
ARB-associated	5 (1)
HAE with C1-INH deficiency	8 (2)
HAE with normal C1-INH	3 (<1)
Acquired angioedema with C1-INH deficiency	2 (<1)
Histaminergic angioedema	135 (30)
Medication Allergy	74 (16)
Histaminergic NOS	43 (10)
Food Allergy	16 (4)
Insect Sting	2 (<1)
Unknown	179 (40)

ACEI, angiotensin-converting enzyme inhibitor; *HAE,* hereditary angioedema; *C1-INH,* C1 esterase inhibitor; *NOS,* not otherwise specified.

after stratification by involvement of the upper airway with angioedema (OR [1.85]; 95% CI, 1.07-3.20).

We developed a multivariable model using a prespecified list of candidate predictor variables (Table 4). ACEI or angiotensin II receptor blockers (ARB) use (OR [60.9]; 95% CI, 23.16-160.14) and presentation one hour or more from symptom onset (OR [5.91]; 95% CI,1.87-18.70) were associated with nonhistaminergic angioedema syndromes. Urticaria (OR [0.05]; 95% CI, 0.02-0.15), dyspnea (OR [0.23]; 95% CI, 0.08-0.67), and periorbital or lip angioedema on physical examination (OR [0.25]; 95% CI, 0.08-0.79 and OR [0.32]; 95% CI, 0.13-0.79, respectively) were inversely associated with nonhistaminergic angioedema.

DISCUSSION

We describe the clinical features, management, and outcomes of a large, 10-year cohort of adult patients with angioedema presenting to a quaternary-care ED setting. Among 450 ED presentations for angioedema, 30% represented suspected nonhistaminergic angioedema, 30% represented suspected histaminergic angioedema, and in the remaining patients the etiology could not be definitively categorized. Half of the patients in our cohort were evaluated by an allergist-immunologist after ED care. As compared to histaminergic angioedema, nonhistaminergic angioedema was associated with ACEI medication use, earlier symptom onset relative to ED arrival, tongue and soft palate swelling, and ICU admission, and was inversely associated with periorbital angioedema, lip angioedema, dyspnea, and urticaria.

Our patients had a mean age of 57 years and a subtle female predominance, comparable to existing published cohorts of patients with angioedema.[2,9,14,28,29] Nonhistaminergic angioedema represented 30% of our cases, which is consistent with previous reports of ACEI-induced angioedema comprising 30-40% of angioedema cohorts.[8,9,11] We were unable to identify an etiology of angioedema in 40% of our population. This finding is comparable to reports of angioedema of unknown etiology representing 30-50% of angioedema patients in similar cohorts.[3,13,14] We did not assume a patient to have nonhistaminergic angioedema based upon the use of an ACEI or ARB medication alone. Existing studies have differed in regard to the assignment of ACEI-associated angioedema, whether based upon the presence of ACEI [30,31] or assigned by documented clinician or investigator judgment during chart review.[2,5,8,9,14] We chose to use the judgment and diagnosis assigned by the clinician upon discharge or, when possible, allergist-immunologist at follow-up. Given our approach, ACE inhibitors and ARB medications were taken by some patients with angioedema categorized as histaminergic or unknown etiology. In support of this approach is our observation that approximately 20% of patients in the histaminergic category were using an ACEI or ARB in the overall ED cohort and among the subset of patients who had allergy-immunology consultation.

In a multivariable analysis of the subset patients with suspected nonhistaminergic and histaminergic angioedema, we identified use of an ACEI or ARB medication and the presence of urticaria as the strongest associations with these subgroups, respectively. Time of onset one hour or more from ED presentation was associated with nonhistaminergic angioedema; and dyspnea and angioedema involving the periorbital region or lips were associated with histaminergic syndromes. That urticaria, present in 26% of the overall cohort, is associated with a suspected histaminergic etiology of angioedema is expected; however, we identified patients with suspected nonhistaminergic angioedema and angioedema of unknown etiology who also exhibited urticaria (7% and 26%, respectively). These findings, which could raise concern about the accuracy of classification of angioedema patients, have been noted in similar, published angioedema cohorts.[32] Felder and colleagues noted approximately 30% of those with angioedema of unknown etiology and 9.1% of patients with angioedema secondary to C1-INH deficiency were noted to have urticaria at presentation, and only slightly lower prevalence among those with ACEI-associated angioedema.[32] It is also possible that erythema marginatum, sometimes seen in nonhistaminergic angioedema, could be mistaken for urticaria by clinicians.[33]

The rate of tracheal intubation was 7% among all patients presenting to our ED with angioedema. The rate of

Table 3. Univariable associations with final etiology: nonhistaminergic versus histaminergic angioedema.

Feature*	n=271 OR (95% CI)	P-value	Feature*	n=271 OR (95% CI)	P-value
Age at visit	1.47 (1.26-1.71)†	<0.001	Urticaria	0.08 (0.04-0.18)	<0.001
Sex			Wheezing	0.43 (0.16-1.18)	0.10
Female	1.0 (reference)		Objective location of angioedema		
Male	1.11 (0.69-1.80)	0.66	Face	0.92 (0.54-1.56)	0.76
Race			Periorbital	0.27 (0.14-0.53)	<0.001
White	1.0 (reference)		Lips	0.53 (0.32-0.86)	0.011
African-American	1.51 (0.48-4.75)	0.48	Uvula	1.40 (0.54-3.59)	0.49
All others	0.29 (0.09-0.92)	0.035	Soft palate	9.50 (1.19-76.02)	0.034
Comorbidity			Pharynx	1.27 (0.57-2.83)	0.56
Angioedema history	0.98 (0.60-1.61)	0.93	Tongue	2.50 (1.51-4.14)	<0.001
COPD	3.47 (1.23-9.75)	0.019	Larynx	1.34 (0.45-3.98)	0.59
Asthma	1.14 (0.55-2.39)	0.72	Limbs	0.75 (0.32-1.76)	0.50
Hypertension	17.57 (8.83-34.95)	<0.001	Treatment		
Diabetes	2.36 (1.34-4.17)	0.003	H1 antihistamine	0.62 (0.34-1.12)	0.11
Medications			H2 antihistamine	0.96 (0.59-1.54)	0.86
Neither	1.0 (reference)		Epinephrine	0.77 (0.47-1.26)	0.29
ACEI, ARB, or ACEI and ARB	39.67 (19.43-81.0)	<0.001	Corticosteroid	0.58 (0.31-1.09)	0.090
Transfer from another hospital	2.75 (0.95-7.94)	0.062	Nebulized albuterol	0.69 (0.32-1.47)	0.33
Transport by EMS	1.09 (0.59-2.02)	0.78	Intubation	2.12 (0.87-5.13)	0.10
Time of onset			Disposition		
In the ED or <1 hour	1.0 (reference)		Home	1.0 (reference)	
≥1 hour	3.95 (1.91-8.16)	<0.001	ED observation	0.85 (0.48-1.52)	0.58
Presenting symptoms			Hospital admission	0.70 (0.32-1.53)	0.36
Hoarseness	0.65 (0.18-2.36)	0.51	ICU admission	2.28 (1.12-4.66)	0.024
Voice change	1.80 (0.93-3.47)	0.080	Disposition		
Drooling	1.68 (0.39-7.17)	0.48	Home/ED observation/ hospital admission	1.0 (reference)	
Shortness of breath	0.64 (0.33-1.23)	0.18	ICU admission	2.58 (1.35-4.93)	0.004

*Only select features of interest present in >5 patients were included in the modeling.
†Odds ratios and 95% confidence intervals represent a 10-unit increase.
COPD, chronic obstructive pulmonary disease; *ACEI,* angiotensin-converting enzyme inhibitor; *ARB,* angiotensin II receptor blockers; *EMS,* emergency medical services; *ED,* emergency department; *ICU,* intensive care unit.

tracheal intubation among published angioedema cohorts ranges from 5-35%.[2,3,5,8,9,13,30,34,35] Our findings are consistent with cohorts of patients presenting with angioedema to an ED setting.[9,34] Studies that have identified patients treated for angioedema in a hospital system by diagnosis-related group code, not exclusive to an ED population, have reported higher rates of tracheal intubation.[2,3,8,13] This is expected given inclusion of patients directly admitted from other facilities for ICU care. Studies focusing on admitted patients with angioedema have expectedly reported higher intubation rates.[5,30,35] Zirkle and Bhattacharyya found an intubation rate of 34.8% among their cohort of admitted patients, modestly higher than an intubation rate of 24.6% among admitted patients in our cohort.[35]

Smith and colleagues, in a study examining the burden of angioedema on EDs in the United States, demonstrated tracheal intubation to be a predictor of angioedema due to antihypertensive medication effect.[29] McMormick and colleagues reported ACEI use as a significant predictor of

Table 4. Multivariable associations with final etiology: nonhistaminergic versus histaminergic angioedema.

Feature*	n=271 OR (95% CI)	P-value
Medications		
Neither	1.0 (reference)	
ACEI, ARB, or ACEI and ARB	60.90 (23.16-160.14)	<0.001
Time of onset		
In the ED or <1 hour	1.0 (reference)	
≥1 hour	5.91 (1.87-18.70)	0.003
Presenting symptoms		
Shortness of breath	0.23 (0.08-0.67)	0.007
Urticaria	0.05 (0.02-0.15)	<0.001
Objective location of angioedema		
Periorbital	0.25 (0.08-0.79)	0.018
Lips	0.32 (0.13-0.79)	0.013

*Only select features of interest present in >5 patients were included in the modeling.
OR, odds ratio; *CI,* confidence interval; *ACEI,* angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; ED, emergency department.

airway intervention.[30] Tracheal intubation rates did not differ by etiology in our cohort.

Patient disposition following ED evaluation differed based upon suspected etiology in our univariable analysis, with nonhistaminergic angioedema patients more frequently requiring ICU care. Ishoo and colleagues found that nearly half of ACEI-associated angioedema patients were admitted to the ICU.[3] Our lower rate of ICU admission may reflect increased utilization of ED observation units, 32% among our cohort, for this population over the past 15 years.[16,36] Banerji and colleagues reported a rate of observation admission and subsequent discharge of 18% among angioedema patients presenting to academic EDs between 2003 and 2005.[9] Chiu and colleagues noted a slightly higher admission rate in patients with ACEI-induced angioedema, although this difference was not statistically significant.[2] An association between nonhistaminergic angioedema and admission to an ICU level of care is logical, given a predilection of ACEI-associated angioedema to involve the upper airway[9,10,17,37] and the association between upper airway involvement and ICU admission.[5] In an analysis stratified by upper airway involvement, we found that patients with nonhistaminergic angioedema remained more likely to require ICU admission. This finding may be due to the relatively prolonged duration of ACEI-associated angioedema and its refractory nature to conventional therapies as compared to histaminergic angioedema.

LIMITATIONS

We conducted our study at a single academic institution; thus, additional research is needed to determine the applicability of our findings to other settings. The retrospective design led to the inherent limitation of obtaining data from an existing medical record. We developed and used a standardized data abstraction tool and created rules related to each data field to minimize inconsistency. We obtained our cohort by searching for ICD-9 codes related to angioedema as have been used in prior studies, and it is possible that this approach may have led to missed cases of angioedema. We categorized patients broadly into histaminergic, nonhistaminergic, or unknown based upon available documentation. Patients in the unknown category lacked compelling evidence at the time of presentation, during hospital admission, or upon follow-up to allow for determination of suspected etiology. Our findings might have been different if we knew with certainty into which group these patients fell; however, the trichotomy we have described approximates the uncertainty experienced in clinical practice and is similar to other reported cohorts.[3]

As our study was observational and retrospective, few patients had C4, tryptase, or C1-INH levels obtained. This is a limitation also present in most existing published ED cohorts. Future, prospective, ED-based studies would benefit from obtaining C4 and tryptase levels at the point of care to better ensure the precision of etiology determination. For example, it is possible that an ACEI might unmask a previously undiagnosed case of HAE or acquired angioedema, although the categorization of nonhistaminergic would remain unchanged. Lastly, our patient population includes a smaller number of African-American patients as compared to previously reported cohorts. Given the 3–4.5 fold increased incidence of ACEI-associated angioedema in African-Americans, our findings may not be generalizable to populations with differing demographics.

CONCLUSION

In a large cohort of angioedema patients presenting to a quaternary-care ED, similar frequencies of nonhistaminergic angioedema and histaminergic angioedema were noted, and in 40% of patients an etiology could not be established. Among patients with an identified etiology of angioedema, ACEI medication use and urticaria were the strongest predictors of nonhistaminergic and histaminergic angioedema, respectively. As compared to histaminergic angioedema, patients with nonhistaminergic angioedema were more likely to present for care more than one hour from symptom onset, and less likely to present with dyspnea or angioedema of the periorbital region or lips. Identification of these characteristics upon presentation may guide emergency providers in initiating empiric treatment.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Emergency Reversal of Anticoagulation

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Section Editor: Michael Abraham, MD
Submission history: Submitted March 11, 2018; Revision received May 24, 2019; Accepted May 28, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2018.5.38235

Owing to the propensity of anticoagulated patients to bleed, a strategy for reversal of anticoagulation induced by any of the common agents is essential. Many patients are anticoagulated with a variety of agents, including warfarin, low molecular weight heparin, and the direct oral anticoagulants such as factor Xa and factor IIa inhibitors. Patients may also be using antiplatelet agents. Recommendations to reverse bleeding in these patients are constantly evolving with the recent development of specific reversal agents. A working knowledge of hemostasis and the reversal of anticoagulation and antiplatelet drugs is required for every emergency department provider. This article reviews these topics and presents the currently recommended strategies for dealing with bleeding in the anticoagulated patient. [West J Emerg Med. 2019;20(5)770-783.]

INTRODUCTION

Inappropriate bleeding is the most concerning complication of anticoagulant therapy. The risk of bleeding varies with the type of anticoagulant agent used.[1] The incidence of bleeding while on warfarin has been estimated at 15-20% per year, with life-threatening bleeding occurring at a rate of 1-3% per year.[2] In 2010, atrial fibrillation alone prompted about 30 million prescriptions for warfarin.[2] This does not include the many additional disease processes for which warfarin was indicated. In addition, the use of the direct oral anticoagulants (DOACs), such as factor Xa and factor IIa (thrombin) inhibitors, is rapidly increasing. Compared to warfarin, these drugs have generally been associated with lower rates of major hemorrhage and a reduction in the risk of fatal bleeding and intracranial hemorrhage (ICH).[3] Owing to the propensity of anticoagulated patients to bleed, a strategy for reversal of anticoagulation induced by any of the common agents is essential for the treating clinician. We will review physiologic hemostasis processes, the effect of anticoagulation on normal hemostasis, and then discuss each anticoagulant and its reversal.

Providers should remember that all patients with emergent or life-threatening bleeding require attention to basic interventions, including cessation of anticoagulation therapy, blood product transfusions, and assessment for airway protection. Mechanical methods of hemostasis may be necessary, including direct compression, surgery, or embolization.

Normal Hemostasis

Hemostasis occurs as part of a tightly regulated balance between clot formation and clot breakdown. Clot formation develops through an interaction of two independent processes—primary and secondary hemostasis. While the emergency physician does not need to have an intimate familiarity with all the details of the coagulation cascade, basic principles can guide the understanding of anticoagulants and reversal.

Primary Hemostasis

When damaged vascular endothelium is exposed, platelets bind with a glycoprotein binding complex (GPIIbIIIa) on the platelet and von Willebrand factor (vWF) on the endothelium. Platelets are then activated and release serotonin, platelet activating factor, platelet factor 4, thromboxane A2, and other substances, which attract, activate, and facilitate aggregation of other platelets.[4] Primary hemostasis depends on platelet count and platelet function. Medications such as aspirin, nonsteroidal anti-inflammatory drugs, and others can inhibit platelet aggregation for varying durations. Platelet function testing reveals problems with platelet activity but is not done in real time so as to be useful in the emergency department (ED) setting.

Secondary Hemostasis

This involves the generation of fibrin as a result of activation of the clotting cascade. Two pathways exist to initiate the

cascade: the tissue factor (TF) pathway (formerly called the extrinsic pathway) and the contact activation pathway (formerly the intrinsic pathway) (Figure 1). The TF pathway is activated when an injury to the blood vessel allows factor VII (FVII) to come in contact with TF, which is expressed on stromal fibroblasts and leukocytes. The FVII-TF complex activates the common pathway leading to a large thrombin burst. This pathway is more clinically important as it generates the most fibrin in the shortest time. The contact activation pathway is initiated when collagen in the basement membrane of a blood vessel is exposed and a complex of high-molecular-weight kininogen (HMWK), prekallikrein, and FXII is formed. This causes the sequential activation of factors activating the common pathway culminating in fibrin formation. This pathway is less important in coagulation, but it plays a significant role in inflammation and innate immunity.

Fibrin crosslinks platelets, strengthening the primary platelet plug. For the system to function properly, there has to be an adequate quantity of functional clotting factors. Secondary hemostasis is tested by measuring the prothrombin time (PT) and the partial thromboplastin time (PTT) (Table 1).

Impact of Anticoagulation Agents and Other Factors on Normal Hemostasis

Despite the complexity of the coagulation cascade, a basic familiarity with five coagulation factors (II, VII, VIII, IX, X) can explain almost all of the clinically relevant aspects of coagulation, anticoagulation and its reversal. For completeness, Factor VIII is included here because of its relevance to inherited clotting disorders: Factor VIII deficiency (hemophilia A) and Factor IX deficiency (hemophilia B). Patients with either of these diseases may present with bleeding (Table 1 and Figure 2). Commonly available tests include a PTT, PT, and international normalized ratio (INR) – a way of standardizing PT measurement across labs. Anti-Xa activity, thrombin time (TT), and ecarin clotting time (ECT) tests are often not readily available in the ED setting.

Activated Partial Thromboplastin Time (aPTT)

The aPTT is a measure of the contact activation (intrinsic) coagulation pathway; aPTT becomes prolonged in patients on heparin. It is not, however, a reliable measurement of anticoagulation in patients on low-molecular-weight heparin (LMWH) and with synthetic heparin chains such as fondadarinux (Arixtra) (a synthetic pentasaccharide). PTT will be prolonged in patients who are taking the factor II inhibitor dabigatran (Pradaxa). With increasing dabigatran plasma concentration, however, the response is curvilinear and flattens at higher dabigatran levels. These non-linear levels cannot be used to quantify effect. Therefore, the aPTT helps to identify that the patient has recently taken dabigatran but cannot assess the clinical degree of anticoagulation.[5,6] A normal aPTT, in conjunction with a normal TT, excludes any clinically relevant anticoagulant activity of the drug.[7]

Prothrombin Time (PT)

PT and INR represent the changes to the TF (extrinsic) and common pathways. INR is prolonged with the use of warfarin. PT can also be prolonged with the use of rivaroxaban (Xarelto), an anti-Xa agent. The magnitude of PT/INR elevation, however,

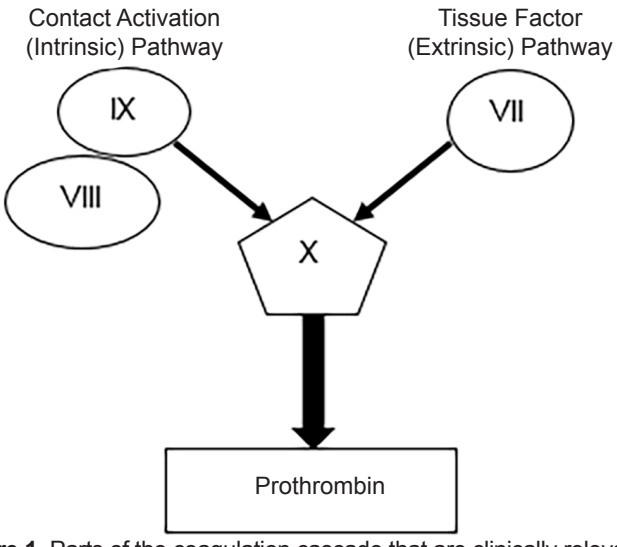

Figure 1. Parts of the coagulation cascade that are clinically relevant to the emergency physician.

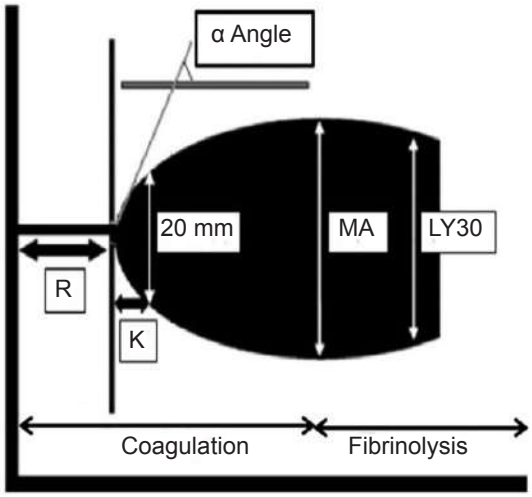

Figure 2. Thromboelastography (TEG)/rotational thromboelastometry graphic.
R, reaction time, represents the time until initial fibrin formation. R reflects the coagulation factor levels present in the individual; *K*, coagulation time, from R until the amplitude of the TEG reaches 20 mm; *MA,* maximum amplitude, describes the maximum strength of the clot and reflects platelet function and fibrinogen activity; *α* angle, measures the speed of fibrin accumulation and cross linking and assesses the rate of clot formation; *LY30*, percentage diminution of the amplitude at 30 minutes after the maximum amplitude has been reached. LY30 represents a measure of the degree of fibrinolysis.[10]

Table 1. Laboratory testing of hemostasis.

Test	Range	Components Tested	Medications
Prothrombin Time (PT/INR)	12-13 sec/0.8-1.2	Tissue factor pathway and common pathway (II, VII, X)	Warfarin, anti-Xa agents (rivaroxaban*, apixaban*, edoxaban*)
Partial Thromboplastin Time (PTT)	30-60 seconds	Contact activation and common pathways (all factors except factor VII)	Heparin, factor II inhibitors (dabigatran**)
Anti-Xa Assay	0.0	Factor X	LMWH, anti-Xa agents (rivaroxaban*, apixaban*, edoxaban), fondaparinux
Thrombin Time	12-14 seconds	Factor II activity	Factor IIa inhibitors (dabigatran)
Ecarin Clotting Time (ECT)	22.6 to 29.0 seconds At trough: >3x the upper limit of normal suggests bleeding risk	Factor II activity	Factor IIa inhibitors (dabigatran)

PT/INR, prothrombin time/international normalized ratio; *LMWH*, low-molecular-weight heparin.
*PT is frequently elevated with these agents but a prediction as to the degree of anticoagulation is unreliable with these agents.
**PTT is useful in determining the presence of an anti-factor II activity, however it cannot be used to monitor the degree of anticoagulation produced by these medications.

is not an effective measure of anticoagulation. PT/INR are very insensitive for detecting or predicting anticoagulation with the other anti-Xa agents apixaban (Eliquis) or edoxaban (Savaysa).[7,8] Therapeutic dabigatran levels may slightly elevate the INR, but INR levels do not correlate with dabigatran activity.

Anti-Factor Xa Activity Assay

For these agents that primarily act on factor X, including the direct anti Xa agents, LMWH and fondaparinux, anti-Xa activity levels can be measured. Because it usually cannot be obtained in real time, the assay is rarely useful to make decisions in the ED setting.

Thrombin Time and Ecarin Clotting Time (ECT)

Thrombin clotting time directly assesses factor II activity by reflecting the conversion of fibrinogen to fibrin, while ECT assays test for factor II generation and has a strong linear correlation with the plasma concentrations of dabigatran. Both directly measure the activity of direct factor IIa inhibitors.[5,9] Similar to the anti-factor Xa activity assay, these tests are not readily available or used in the clinical setting.

Thromboelastography

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are functional tests of coagulation that measure the interaction of clotting factors, fibrinogen, and platelets. The test determines the viscoelasticity of the clot during formation and breakdown. The whole blood sample is placed in a cup in which a pin is suspended from a torsion wire. The wire is connected to a mechanical-electrical transducer. As clotting progresses, increased tension in the coagulating blood alters the rotation detected by the pin. In TEG the cup is rotated, and in ROTEM the pin is rotated. These changes are converted into electrical signals, which then form a graphical representation (Figure 2). Measurements of the different phases of clotting and subsequent fibrinolysis are shown as changing of the shape of the graphic (Figure 3).[10] Although TEG and ROTEM use slightly different nomenclature, the results are interchangeable.

TEG/ROTEM, in addition to the INR and PTT, can augment the understanding of the patient's overall coagulation picture and help guide the need for transfusion of various blood products. There is growing interest in the use of TEG/ROTEM in trauma and other ED patients to assess the patient's entire clotting process.[11]

Reversal of Anticoagulation

Reversal of Warfarin

Warfarin inhibits hepatic synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X.[12] This occurs through inhibition of vitamin K epoxide reductase and vitamin K1 reductase, which deplete vitamin HK2 (hydroquinone) and limit gamma-carboxylation of regulatory anticoagulant proteins C and S, as well as vitamin K-dependent coagulation (Figure 4).[13]

Vitamin K1 (phylloquinone) allows for the synthesis of vitamin K-dependent clotting factors de novo, while fresh frozen plasma (FFP) and prothrombin complex concentrates (PCCs) provide supplemental coagulation factors, including proteins C and S in some preparations. Vitamin K may be administered orally or intravenously. Due to erratic absorption, vitamin K should never be given via subcutaneous or intramuscular routes. Although the intravenous (IV) route has been associated with anaphylactoid reactions, the incidence of such reactions is extremely low (3/10,000).[15] To further decrease the risk, it is advised to administer IV vitamin K over at least 20 minutes.[16]

When given intravenously, the INR begins to decrease within 1-2 hours[16] and peaks in 4-6 hours.[17] The 2012 American College of Chest Physician Guidelines recommend

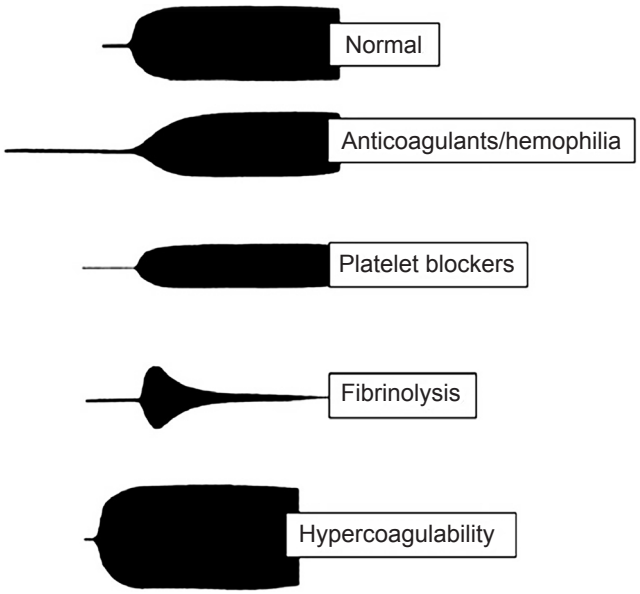

Figure 3. Interpretation of thromboelastography/rotational thromboelastometry graphics.[10]

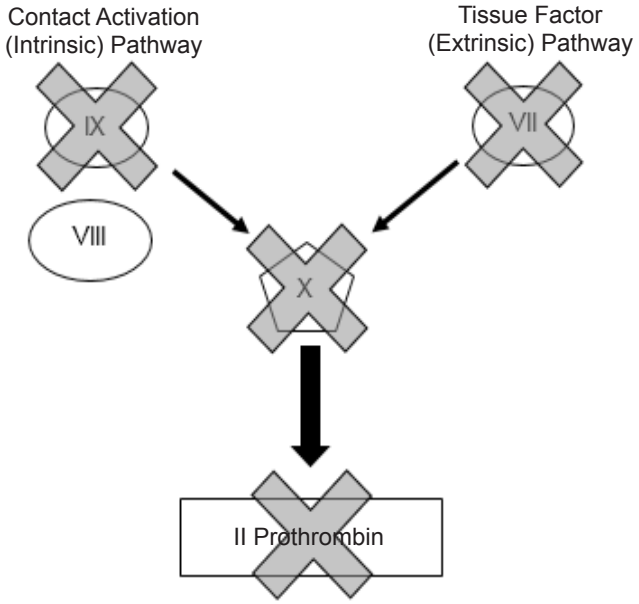

Figure 4. Where warfarin works.

10 milligrams (mg) of IV vitamin K for patients with life-threatening or emergent bleeding. See Table 2 for a summary of the 2012 Chest guidelines for reversal of Vitamin K antagonists.

FFP is derived from donor plasma that is rapidly frozen and stored at 18°C or colder.[16] It contains all coagulation factors, as well as fibrinogen, protein C, and vWF. The intrinsic INR of FFP is 1.5, and it has not shown clinical benefit in patients with an INR below 1.7. Each unit of FFP has a volume of 200-250 milliliters (mL).[12] Onset of action is 13-48 hours after administration. When FFP is ordered, it must undergo ABO blood group compatibility testing; Rh compatibility is not required. The plasma may take up to an hour to thaw, and then must be transfused urgently, as the labile clotting factors degrade with time.[16] Human immunodeficiency virus and hepatitis transmission are known risks of transfusion, as well as the development of transfusion-related acute lung injury (TRALI) and allergic reactions.[16]

FFP is relatively cheap and widely available. However, administration is cumbersome. Dosing for life-threatening hemorrhage is 10-15 mL per kilogram of FFP, which averages to 4-5 units (800-1,250 mL) in an average-sized adult patient.[16] FFP remains in the intravascular space and can precipitate fluid overload, and the evidence for its efficacy is only of low quality. Stanworth et al. noted that the reduction in INR was approximately 0.2 in 5000 FFP transfusions, performed for a broad range of indications.[18]

PCCs contain nonactivated coagulation factors II, VII, IX, and X, with varying amounts of proteins C and S. Both three- and four-factor concentrates contain these four factors. However, three-factor PCC contains lower (possibly negligible) amounts of factor VII.[16] The concentrates are stored as a powder and may be reconstituted within minutes into a volume <100 mL.[12] There are multiple dosing strategies, including a combination of INR and weight-based dosing, INR-based, and as a fixed dose. Onset of reversal occurs within 10-30 minutes, with an immediate decrease in INR to less than 1.5.[19] Duration is 12-24 hours, and co-administration of vitamin K prevents rebound anticoagulation.[16]

PCC is administered as a small volume, has a quick onset, and results in immediate decrease in INR. The risks of TRALI and volume overload with FFP transfusions are eliminated. However, there is no significant evidence that PCC improves clinical outcomes or that it is superior to FFP, and it may be cost-prohibitive. A small risk of a prothrombotic state was established through a meta-analysis of 27 observational studies including 1032 patients. Twelve thromboembolic complications occurred (1.4%), two of which were fatal.[20] A recent comparison of 4-factor PCCs to FFP has shown that the risk of inappropriate thrombosis is roughly the same.[21]

Recombinant factor VII, rVIIa (NovoSeven) is not recommended as a warfarin reversal agent.[22,23,24] See Table 3 for a summary and dosing of reversal agents for warfarin.

Heparin Reversal

As reviewed by Hirsh and Raschke, unfractionated heparin binds to antithrombin through a high-affinity pentasaccharide.[25] This complex then binds to factor II, irreversibly inhibiting factor II's procoagulant activity, as well as coagulation factors Xa, IXa, XIa, and XIIa. The half-life of heparin is approximately 60 minutes.

Low-molecular-weight heparins (LMWH) are prepared by depolymerizing heparin. LMWH indirectly inhibits factor Xa activity by activating the antithrombin III complex,

similar to heparin. This complex then inactivates factor Xa (Figure 5). These drugs also have a variable effect on factor II (prothrombin), with an anti-Xa to anti-II ratio that varies from 3:1 to greater than 5:1. The subcutaneous elimination half-life is 3-6 hours after injection and is not dose-dependent.[25]

Fondaparinux is a synthetic pentasaccharide that serves as a highly selective factor Xa inhibitor. It selectively binds to antithrombin III to inhibit factor Xa. Unlike heparin or LMWH, it does not inhibit factor II. There is rapid and complete bioavailability, and elimination half-life is 17-21 hours.[26]

Heparin is reversed by protamine, but protamine incompletely reverses factor Xa inhibition of LMWH despite complete neutralization of the antithrombin effect. This results in only about a 60% reversal of LMWH effects. If LMWH has been administered within the prior eight hours, 1 mg of protamine will neutralize 1 mg of enoxaparin.[27] More than 50 mg of protamine will cause some anticoagulation by inhibition of factor V and is not recommended.

There is a paucity of human data on the reversal of fondaparinux. Human volunteer and animal studies suggest that recombinant activated factor VII may have some ability to partially normalize markers of anticoagulation in vivo.[28] Activated PCC (aPCC), also known as "factor VIII inhibitor bypassing activity" (FEIBA), has been shown in animals to lessen bleeding and correct endogenous thrombin potential, which represents the amount of thrombin that can be generated after coagulation is activated by tissue factor in vitro.[29] aPCC contains variable amounts of activated clotting factors with most of the activation occurring with factor VII.

Both andexanet alfa (a recombinant factor Xa)[30] and ciraparantag[31,32] (also known as aripazine) have been shown to bind to Xa inhibitors, but meaningful human studies on heparin,

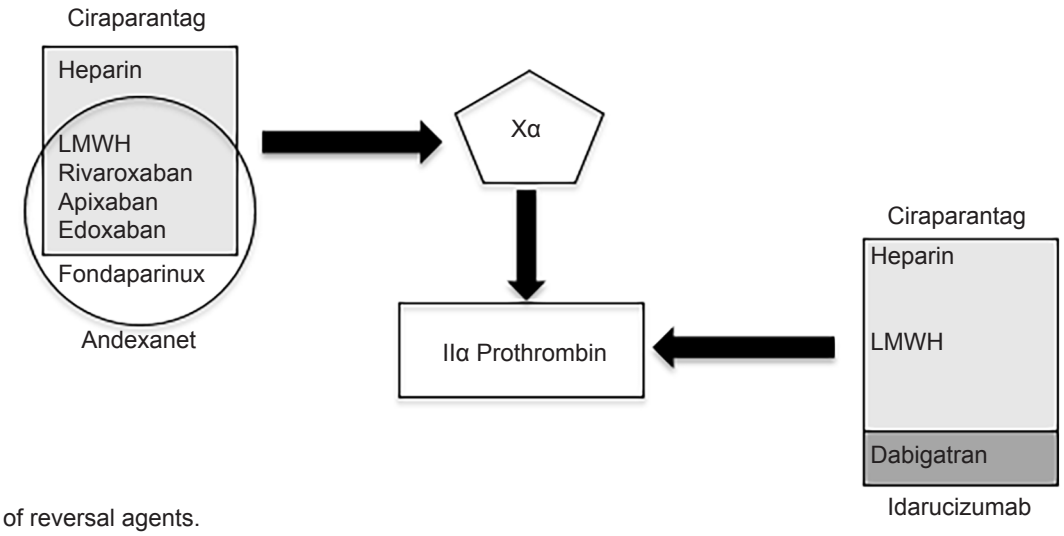

Figure 5. Actions of reversal agents.

Table 2. Recommendations for managing increased international normalized ratios or bleeding in patients rreceiving Vitamin K antagonists.

Condition	Description
INR above therapeutic range but <5.0; no significant bleeding	Lower dose or omit dose, monitor more frequently, and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required.
INR ≥5.0 but ≤10.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at lower dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K1 (1-2.5 mg orally), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 (2–4 mg orally) can be given with the expectation that the INR will decrease in 24 hours. If the INR is still high, additional vitamin K1 (1–2 mg orally) can be given.
INR >10.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K1 (5–10 mg orally) with the expectation that the INR will be reduced substantially in 24–48 hours. Monitor more frequently, and use additional vitamin K1 if necessary. Resume therapy at lower dose when INR therapeutic.
Serious or life-threatening bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K1 (10 mg by slow IV infusion), supplemented with 4-factor prothrombin complex concentrate or fresh frozen plasma. Vitamin K1 can be repeated every 12 hours.

* Adapted from Holbrook A, et al. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e152S-184S.

Table 3. Summary and dosage of reversal agents for warfarin in life-threatening bleeding.

Agent	Dose	Additional Information
Vitamin K	1-10 mg IV	SC delivery is no longer used
PCC 3-Factor (Profilnine) 4 factor (Kcentra*)	Strategy 1: INR and Weight-Based Dosing •INR 2-4: 25 IU/kg by IV push •INR ≥4-6: 35 IU/kg by IV push •INR >6: 50 IU/kg by IV push Strategy 2: INR-Based Dosing •INR <5: 500 units; INR ≥5: 1000 units Strategy 3: Fixed Dose •1500 IU	INR-based dosing is most effective with 3-factor preparations. Absolute dosing strategies should not be used with 3-factor PCCs. Any of the 3 strategies can be used with 4-factor PCCs.

mg, milligram; *SC*, subcutaneous; *PCC*, prothrombin complex concentrate; *INR*, international normalized ratio; *IU*, international unit; *IV*, intravenous; *kg*, kilogram.
*U.S. Food and Drug Administration-approved for the reversal of warfarin-related bleeding.

LMWH, and fondaparinux anticoagulated patients are lacking. See Table 4 for a summary of reversal agents for heparin, LMWH and fondaparinux.

Direct Oral Anticoagulants (DOACs)

DOACs are so named because they work by binding directly to factor Xa or factor II without the need to first complex with antithrombin (Figure 6). These agents were previously known as novel oral anticoagulants (NOACs), but the term "direct" is more appropriate. Two categories of agents are currently in use: direct factor IIa inhibitors (also called "direct thrombin inhibitors" or DTIs) such as dabigatran (Pradaxa) and the factor Xa inhibitors, including apixaban (Eliquis), rivaroxaban (Xarelto), edoxaban (Savaysa), and betrixaban (Bevyxxa).

Non-specific reversal agents in the form of 4-factor PCC (Kcentra in the United States) and aPCC (FEIBA) attempt to supplement the coagulation system with multiple clotting factors in hope of overwhelming the effect of the dabigatran. They are often considered when a specific reversal agent, idarucizumab (Praxbind) is not available. aPCC has been shown to reduce bleeding resulting from dabigatran in animal models[40] and in healthy volunteers.[35,39,41] Factor VIIa has shown mixed results in human volunteers.[42, 43] In the absence of idarucizumab, FEIBA is the agent of choice when dabigatran reversal is needed.

A Specific Antidote

Idarucizumab (Praxbind) is a monoclonal antibody fragment that binds free and factor IIa-bound dabigatran. Dabigatran binds to idarucizumab with 350 times greater affinity than for factor II.[5,44] It is the only U.S. Food and Drug Administration (FDA)-approved antidote for bleeding related to dabigatran. It is manufactured in 2.5 gram (g) vials, and it is administered as a 5 g total dose intravenously. See Table 5 for dosing of idarucizumab.

Pollack et al. reviewed the results of the prospective Reversal of the Anticoagulant Effects of Dabigatran by Intravenous Administration (RE-VERSE AD) clinical trial. Patients taking dabigatran who had serious bleeding or required urgent procedures were administered idarucizumab, and the results of the first 90 patients were reported. Of these patients with elevated clotting times at baseline, 88-98% had rapid and complete reversal of anticoagulant effects. One of 90 patients had a thrombotic event within 72 hours.[45]

In the 2017 follow-up study by Pollack et al, the full cohort of patients in the RE-VERSE AD clinical trial was analyzed. Two groups were studied. A 5 g dose of idarucizumab was administered to patients who received dabigatran therapy. Group A included 301 patients with life-threatening bleeding (98 patients with ICH and 137 with gastrointestinal [GI] bleeding). Group B included 202 non-bleeding patients requiring an urgent surgical procedure.[46] The maximum percentage reversal of dabigatran was 100% (95% confidence interval, 100 to 100), as determined by diluted thrombin time (dTT) or ECT.[46] ECT and dTT were chosen because they correlate linearly with dabigatran concentrations measured by mass spectroscopy. The article also reports a good correlation between these tests and the readily available aPTT.

In Group A, median time to cessation of bleeding among patients with ICH was 11.4 hours, and with GI bleeding was 3.5 hours. In Group B, the median time to procedure was 1.6 hours. The peri-procedural hemostasis was identified as normal by the treating clinician (using the International Society of Thrombosis and Haemostasis Bleeding Scale) in 188 patients of 202 patients (93%).[46] At 30 days following idarucizumab administration, a total of 24 patients experienced a thrombotic event (4.8%), three of which were fatal. These included 12 venous thromboembolic events (VTE) including deep vein thrombosis (DVT) and/or pulmonary embolism (PE) or other systemic embolus, six myocardial infarctions, and six strokes. Of note, only 1.8% of the patients in this study were on dabigatran for VTE. The overall 30-day mortality rate was around 13%.[46]

Morbidity and mortality benefits of idarucizumab are unclear and are likely co-dependent on global management of

Table 4. Dosage of reversal agents for heparin, low-molecular-weight heparins, and synthetic pentasaccharides—fondaparinux (Arixtra).

Agent	Dose	Additional Information
Protamine for Heparin	Time elapsed from last heparin dose: Dose of protamine (mg) to neutralize 100 units of heparin Immediate: 1-1.5 mg/100 units heparin 30-60 min: 0.5-0.75 mg/100 units heparin >2 h: 0.25-0.375/100 Units Heparin	Doses should not exceed 50 mg at a time.
Protamine for LMWH	Dalteparin (Fragmin): 1 mg protamine neutralizes 100 units dalteparin •If bleeding continues or PTT remains prolonged 2-4 hours after protamine, may give a second protamine dose of 0.5 mg per 100 units dalteparin. Enoxaparin (Lovenox): if < 8 hours after last dose enoxaparin, give 1 mg protamine per 1 mg enoxaparin; •If 8-12 hours after last dose enoxaparin, give 0.5 mg protamine per 1 mg enoxaparin. •If >12 hours after last dose of enoxaparin (when enoxaparin administered q12h), protamine not required. •If bleeding continues or PTT remains prolonged 2-4 hours after protamine, may give a second protamine dose of 0.5 mg per 1 mg enoxaparin.	Protamine may have some effect on LMWH. Only 60-75% of the anti Xa activity of LMWH is neutralized by protamine. Effectiveness depends on which LMWH is used. There is a real concern when using protamine with LMWH: Protamine when given by itself has anticoagulant effects. If there is reversal of the non-Xa activity and only partial (but not enough) reversal of the Xa activity, the net vector will point to anticoagulation. DO NOT EXCEED 50 mg per dose. Protamine only partially neutralizes anti-factor Xa activity (~60%). Fondaparinux: Has only anti-Xa activity and protamine will have no significant effect.
Reversal of Fondaparinux	•Recombinant activated factor VII (NovoSeven): 90 mcg/kg IV •Activated prothrombin complex concentrate (aPCC) FEIBA 50 U/kg IV	Very limited data to recommend these agents to reverse fondaparinux.

mg, milligram; *IV*, intravenous; *LMWH*, low-molecular-weight heparin; *PTT*, partial thromboplastin time; *q12h*, every 12 hours; *kg*, kilogram; *FEIBA*, factor VIII inhibitor bypassing activity.

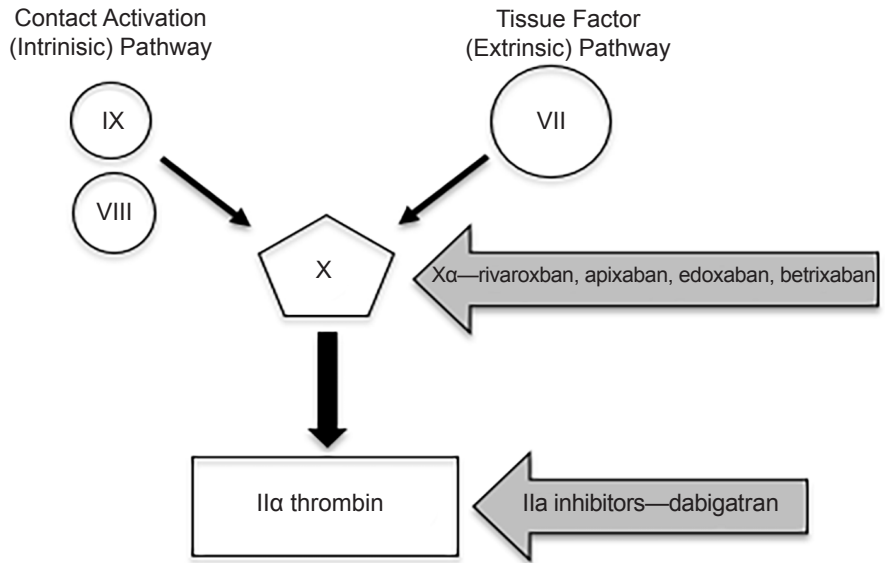

Figure 6. Where direct oral anticoagulants act.

these patients, including supportive care. Future rapid access to dabigatran concentrations may also guide reversal treatment and avoid unnecessary administration to those with low plasma drug levels.[47]

Factor Xa Inhibitors: apixaban, rivaroxaban, edoxaban and betrixaban

Apixaban (Eliquis), rivaroxaban (Xarelto), edoxaban (Savaysa), and betrixaban (Bevyxxa) reversibly and

Table 5. Dosage of reversal agents for dabigatran.

Agent	Dose	Additional Information
aPCC (FEIBA)	50 U/kg	May be more thrombogenic than non-activated PCC.
Antibodies to dabigatran (Idarucizumab)	5 g provided as two separate vials each containing 2.5 g/50 mL.	The only FDA-approved "antidote" to dabigatran-related bleeding.
Cryoprecipitate	2 bags	If fibrinogen is < 200 mg/dL, give 2 bags cryoprecipitate.

aPCC, activated prothrombin complex concentrate; *FEIBA*, factor VIII inhibitor bypassing activity; *U/kg*, units per kilogram; *g,* gram; *mL*, milliliter; *FDA*, U.S. Food and Drug Administration; *mg/dL,* milligrams per deciliter.

competitively inhibit free and clot-bound factor Xa. With the exception of betrixaban, which has a more limited scope of indications, Xa agents are FDA-approved for stroke and systemic embolism prevention in patients with nonvalvular atrial fibrillation and for DVT and PE treatment. Rivaroxaban and apixaban are also approved for DVT prevention after hip or knee replacement surgery and to reduce the risk of recurrent DVT and PE. Betrixiban is approved for prophylaxis of VTE in hospitalized patients who are at significant risk for VTE.[48-50] Median time to peak plasma concentration is approximately two hours for both apixaban and rivaroxaban, with steady-state concentrations reached by day four.[51] The clinical effect of these drugs diminishes over time such that at 18 hours after the last dose, there is no indication for reversal.

Hemodialysis is not likely to be beneficial in cases of anticoagulation from apixaban or rivaroxaban since both of those drugs are more highly protein-bound. While edoxaban has relatively low protein binding, it is not well cleared by dialysis.[52] Betrixaban is 60% protein bound, and it is not known if dialysis effectively clears the drug.[53]

Nonspecific Reversal Agents

The theory behind the use of these nonspecific reversal agents such as FEIBA, PCC, and rFVIIa is that they attempt to overwhelm the effect of a circulating Factor Xa inhibitor by supplementing either upstream factors (rVIIa) or factor X, along with both up and downstream factors. Patients taking Factor Xa inhibitors have normal levels of clotting factors and supplementation (in light of a circulating inhibitor) may not be effective, calling into question the potential efficacy of this strategy. Overall, there is limited patient data to support the use of nonspecific hemostatic agents for Factor Xa reversal, particularly with availability of a specific reversal agent.

Dzik (2015) reviewed the conflicting findings regarding factor Xa inhibitors and PCC use.[54] Eerenberg et al (2011) studied healthy volunteers who took five doses of rivaroxaban over three days and subsequently received saline or a 4-factor PCC (Cofact). The PCC corrected the PT.[38] Zahir et al. (2014) reviewed the effects of healthy volunteers who took a single dose of edoxaban and then took different doses of four-factor PCC (Beriplex). Laboratory testing and bleeding after a punch biopsy were then evaluated. Four-factor PCC reversed edoxaban's effects on bleeding duration and endogenous thrombin potential, with complete reversal at 50 international units (IU)/kg. Effects on prothrombin time were partially reversed at 50 IU/kg.[55] Levi et al. looked at healthy volunteers who took nine doses of rivaroxaban and then were randomly assigned to receive saline, 50 IU/kg 4-factor PCC (Beriplex), or 50 IU/kg of 3-factor PCC. The results showed that while 4-Factor PCC modestly and transiently reversed the PT, measured anti-Xa activity was identical after infusion of saline and 4-factor PCC.[56]

Multiple guidelines suggest PCC may be considered, but there are no definitive recommendations regarding its use.[57-60] Turpie et al. (2012)[59] and Spahn[58] recommend 25-50 IU/kg, while Baumann Kreuziger et al. (2014) suggest 50 IU/kg of PCC.[60] As described above, there is no consistent or significant evidence showing that PCC clinically reverses bleeding in real-world patients who are taking anti-Factor Xa anticoagulants. With the introduction of specific antidotes it is unlikely that PCC will remain a first-line reversal agent.[54] Dosing of PCC and FEIBA for Factor Xa inhibitor reversal are listed in Table 6.

Specific Antidotes

Andexanet alfa, now officially known by the new generic name "coagulation factor Xa (recombinant), inactivated-zhzo," and by the trade name Andexxa, is a specific factor Xa reversal agent. It was approved by the FDA in May 2018 and became commercially available in the first quarter of 2019. Andexanet alfa (we have chosen to use the more familiar and easier generic name) is a recombinant, modified factor Xa-like protein that acts as a "decoy molecule." It binds factor Xa inhibitors with high affinity, yet owing to the designed lack of a membrane-binding carboxyglutamic acid (GLA) domain, it is functionally inactive and cannot participate in coagulation.[61,62]

The initial, healthy volunteer studies of this drug (Annexa-A and Annexa-R) showed rapid reduction of anti-factor Xa activity and restoration of thrombin generation in a total of 100 study subjects compared to 44 patients in the control groups. These patients were all anticoagulated with either rivaroxaban or apixaban and then given either a bolus only of andexanet or a

Table 6. Dosage of nonspecific reversal agents for anti factor Xα anticoagulants (rivaroxaban, apixaban, edoxaban, betrixaban).

Agent	Dose	Additional Information
4-Factor PCC (Kcentra)	25-50 units/kg	Not to exceed 5000 units. Repeat dosing is not recommended. This is generally considered the preferred agent for reversing anti-Xa Inhibitors.
aPCC (FEIBA)	25 units/kg	If still clinically significant bleeding, consider re-dosing, but no sooner than 6 hours.

aPCC, activated prothrombin complex concentrate; *FEIBA,* factor VIII inhibitor bypassing activity; *U/kg*, units per kilogram.

bolus plus infusion. There were no thrombotic events or serious adverse events reported. Minor side effects occurred in 13 patients and were limited to dysgeusia (n = 2), feeling hot (n = 4), flushing (n = 6), and uncomplicated urticaria (n = 1).[30]

The phase 3b-4 study (ANNEXA-4) was published in February 2019. This manufacturer-sponsored study evaluated patients taking factor Xa inhibitors presenting with acute life-threatening or uncontrolled bleeding to assess reduction in anti-Xa activity as well as hemostasis and safety. The study, which included 352 patients with primarily intracranial (64%) or GI (26%) bleeding, showed that andexanet alfa rapidly reduced anti-Xa activity with effective hemostasis as judged by an independent committee using predetermined criteria adapted from those used in efficacy studies of 4-factor PCCs[63] (Table 7). Safety was evaluated in all 352 patients while efficacy was evaluated in 254 patients.

Following administration of the andexanet alfa bolus, the median anti-Xa activity decreased by 92% among patients treated with rivaroxaban (n=100) and apixaban (n=134). This decrease was maintained during the two-hour infusion.[63] Thrombin generation was restored to baseline in 100% of the patients. Hemostasis was evaluated at 12 hours and adjudicated as excellent or good in 82% of patients overall. Specifically, 85% of the GI bleeds and 80% of the intracranial hemorrhages had good or excellent hemostasis. This was well after termination of the two-hour infusion and during the time when the anticoagulant effects were beginning to return as measured by a rise in anti-Xa activity. As the process of forming clots is rapid, it is postulated that a stable clot was formed during the time of infusion when anticoagulation was reversed and this accounted for the hemostatic efficacy despite the short, two-hour duration of infusion. In no cases was the infusion continued for longer than two hours. Optimal dosing using a longer infusion is unclear and not addressed in ANNEXA-4. Further studies will be needed to see if the high cost of the drug can be offset by additional benefits to the patient. See Table 8 for cost of various reversal agents.

Thirty-four patients (10%) receiving andexanet had a thrombotic event by 30 days with 11 events occurring within five days after receiving andexanet. The remaining 23 patients had their thrombotic event during the time period of 6 and 30 days after treatment.[63] These events included myocardial infarction, ischemic stroke of uncertain classification, transient ischemic attack, DVT and PE. Two important caveats should be noted regarding thromboembolic events: 1) Since most thrombotic events occurred after andexanet was cleared and no longer affecting hemostatic function, these thrombotic events are more likely secondary to underlying prothrombotic states for which patients were originally anticoagulated. In ANNEXA-4, significantly more (24%) of the patients enrolled were on anticoagulation for a thromboembolic event as compared to studies of PCCs for Xa inhibitor reversal and idarucizumab for dabigatran.[63,45,64] 2) 26 of the 34 thromboembolic events occurred before the patients were restarted on anticoagulation, and only eight cases developed after anticoagulation was resumed.[63] Our conclusion to this is that hypercoagulable patients have a higher propensity to clot when their anticoagulant is reversed and that the timely reinitiation of anticoagulant therapy is important to mitigate these thrombotic events.

ANNEXA-4 reported an all-cause, 30-day mortality rate of 14% (n = 49), of which 71% (n = 35) were cardiovascular in cause, 24% (n = 12) non-cardiovascular, and 5% (n = 2) of unknown etiology.[63] The study was not designed to compare mortalities directly and they did not report any significance to the overall mortality and ICH mortality data. However, in studies comparing warfarin and rivaroxaban or apixaban for atrial fibrillation, historically the overall mortality is 20% with ICH mortality approaching 50%.[65-67] Dosing of andexanet is shown in Table 9.

Ciraparantag, also known as aripazine or PER977, is a synthetic molecule that binds to unfractionated and LMWHs, as well as fondaparinux, dabigatran, and factor Xa inhibitors.[68] It is thought to create a downstream procoagulant state.[69] Ansell et al. performed a phase I clinical trial of healthy volunteers who were given a dose of edoxaban and then administered aripazine. Anticoagulation was reversed in 10 minutes as shown by decreased whole-blood clotting time, and effects lasted for 24 hours without procoagulant activity.[70] Further human trials are needed to assess clinical outcomes and safety profiles. A direct comparison of the clinical efficacy of ciraparantag versus andexanet alfa has yet to be made. Sites of action of ciraparantag, andexanet, and idarucizumab are depicted in Figure 5.

Table 7. Criteria for determining hemostatic efficacy in patients receiving andexanet.

For intracranial hemorrhage	Slowing in growth of hematoma size at one hour and 12 hours compared to baseline.
For gastrointestinal bleeding	A drop in hemoglobin of less than 10% from baseline at 12 hours was considered good hemostasis.
For visible bleeding	Cessation of bleeding at one-hour post andexanet was considered good hemostasis if bleeding stopped at 4 hours and no additional therapy was required.
For musculoskeletal b leeding	Decrease in pain, no objective signs of ongoing bleeding and absence of further swelling.

Table 8. Cost of reversal agents–based on an 80-kilogram patient.

Generic Drug	Trade Name	Dose	Approximate Cost
Phytonadione	Vitamin K	10 mg IV	$395.00[A]
FFP	N/A	4 units is usual minimum	$1000[B] ($250 each)
4-Factor PCC	Kcentra	25-50 units/kg	$2,540 to $5,080[B]
Activated PCC	FEIBA	25 units/kg	$5,400[B]
Idarucizumab	Praxbind	5 grams	$3,600[C]
Andexanet (Low Dose)	Andexxa	400 mg bolus + 480 mg infusion	$24,750**
Andexanet (High Dose)*	Andexxa	800 mg bolus + 960 mg infusion	$49,500

PCC, prothrombin complex concentrate; *FEIBA*, factor VIII inhibitor bypassing activity; *IV*, intravenous; *units/kg*; units per kilogram; *mg*, miligram.

*High dose rarely used in Annexa-4 study protocol. Predicted to be rarely used in real-life practice.

** New technology add-on payment (NTAP) is available with the maximum NTAP reimbursement of $14,062.50, or 50% of the wholesale acquisition cost of the low dose. NTAP is expected to remain in effect for a period of 2-3 years, until the cost of andexanet alfa is included in the recalibration of the diagnosis related group payment rates.

[A] Phytonadione. https://www.drugs.com/price-guide/phytonadione. 2018.

[B] Wexner Medical Center at The Ohio State University pharmacy data. 2019.

[C] Praxbind. http://www.drugs.com/price-guide/praxbind. 2018.

Table 9. Dosing of andexanet.

		Time Since Last Dose	
Drug	Anti-Xα Dose	<8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	Low Dose
	> 5 mg or Unknown	High Dose	

Low dose, 400 milligrams (mg) at 30 mg/min followed by 4 mg/min for up to 120 min; *high dose,* 800 mg over 30 mg/min followed by 8 mg/min (milligrams per minute) for up to 120 min.

Reversal of Antiplatelet Agents

Aspirin irreversibly inhibits cyclooxygenase (COX)-1 and COX-2 enzymes to cause downstream inhibition of thromboxane A_2, while thienopyridines such as clopidogrel (Plavix), ticlopidine (Ticlid), and prasugrel (Effient) irreversibly inhibit the P2Y12 receptor for adenosine diphosphate (ADP) on platelets, preventing ADP binding and platelet aggregation. Ticagrelor (Brilinta) and cangrelor (Kengreal) reversibly inhibit the ADP receptor, and dipyridamole (Persantine) reversibly inhibits ADP uptake by platelets. There is some controversy on how to manage patients on aspirin, clopidogrel, and other antiplatelet drugs. There are no guidelines for reversal of anti-platelet agents, but one in vitro model showed 2-3 units (4 or 6-packs) or 2-3 single-donor apheresis units of platelets added to plasma from healthy volunteers induced a normalization of platelet function.[71]

Gutermann et al. reviewed available guidelines related to antiplatelet therapy and gastrointestinal hemorrhage.[72] There are no clear, clinical practice guidelines to dictate treatment

of acute, life-threatening bleeding other than discontinuing anticoagulant and antiplatelet therapies. The Platelet Transfusions for Intracerebral Hemorrhage (PATCH) trial reported that platelet transfusion for spontaneous ICH in patients on antiplatelet therapy did not reduce bleeding and led to increased mortality and dependence at three months.[73] Although frequently requested by surgical consultants, there is not enough evidence to make routine platelet transfusion a "standard of care."[74] Desmopressin, or DDAVP, increases endothelial release of vWF and factor VIII. It may be used to reverse the antiplatelet effects of aspirin and clopidogrel. DDAVP was evaluated by a meta-analysis in elective or emergent cardiac surgery in patients on antiplatelet therapy or had measured platelet dysfunction. Its use resulted in 25% less total volume of red blood cells transfused, 23% less blood loss, and a smaller risk of reoperation due to bleeding. There was no decrease in mortality or increase in thrombotic events, however, and DDAVP patients had an increase in clinically significant hypotension. The overall quality of evidence was judged to be low to moderate. Included trials were small, and five of the 10 trials were performed more than 20 years ago.[75] Guidelines from the Neurocritical Care Society and Society of Critical Care Medicine support the use of a one-time 0.4 micrograms per kilogram IV dose of DDAVP in patients on antiplatelet therapy with ICH.[76] Dosage of platelets and DDAVP for antiplatelet reversal are summarized in Table 10.

The reason patients are taking antiplatelet medications should be reviewed. Providers must assess the harm/benefit ratio of reversal, particularly in patients with recent coronary stent placement. In general, patients who received a bare metal stent are advised to stay on antiplatelet agents for one month. Those who received a drug-eluting stent should be on antiplatelet therapy for a minimum of six months, depending on the generation of stent (first or second).[77] The main concern is that these patients have a higher risk of stent thrombosis if antiplatelet therapy is discontinued prematurely.

DISCUSSION

Reversal of anticoagulation requires basic knowledge of underlying physiology of hemostasis, as well as obtaining a thorough history. A key piece of information is the timing of the last dose of anticoagulant agent. This is particularly important for DOAC agents where testing for degree of anticoagulation is not easily obtained or timely. Reversal agents for DOAC drugs are generally not indicated if the last known dose was greater than 18 hours prior to presentation. When real-time anti-Xa activity testing becomes widely available it will be very helpful in guiding the need for reversal when the last known dose is not available. If TEG/ROTEM is available, the results may likewise be helpful in this setting.

One of the most important overriding questions is this: "Does reversal of anticoagulation really have a clinically relevant benefit to the patient?" Most of the literature published on specific reversal agents such as 4-factor PCC, idarucizumab and andexanet focus on the agent's ability to normalize tests of coagulation (INR, PTT, etc). Improvement in predetermined clinical markers of bleeding has been demonstrated by looking at the decrease in hematoma growth and limitation of a drop in hemoglobin. Finally, there are suggestions in the literature, mostly based on observation, that there appears to be less bleeding in patients for whom anticoagulation is reversed. A leap is then often made to imply that less bleeding directly translates into improved morbidity and/or mortality. *A morbidity or mortality benefit, however, has not yet been definitively demonstrated.* It is critical to determine if expensive reversal agents that may promote thrombosis are actually beneficial.

Randomized studies of a particular reversal agent vs placebo in bleeding patients will likely never be performed due to ethical concerns. Future studies should report individual patient data and describe detailed outcomes of patients receiving reversal agents, possibly comparing them to historical controls in the era prior to specific reversal agents. Future directions, including further evaluation of ciraparantag and andexanet alfa, especially regarding morbidity and mortality are hopefully in the pipeline. Additional research into the utility of TEG/ROTEM to guide transfusion of blood products and its effects on mortality are also warranted.

CONCLUSION

Hemostasis is a complex, tightly regulated balance between bleeding and clotting. Through the use of anticoagulant agents, patients can be made to bleed, and with reversal agents (some of which are procoagulants by nature), patients can be forced to clot. In each of these situations, the harms and benefits should be weighed in the best interest of the patient and situation. Hopefully in the near future, safer anticoagulants and more-specific reversal agents will become available, along with easy access to specific testing that can guide our use of these powerful medications.

Table 10. Summary and dosage of reversal agents for platelet inhibitors—aspirin, clopidogrel, prasugrel, ticagrelor and nonsteroidal anti-inflammatory drugs.

Agent	Dose	Additional Information
Platelet transfusion	2-3 U of pooled platelets or 2-3 Apheresis U	Human studies proving the efficacy of the use of platelets in patients with anti-platelet agent induced bleeding are lacking.
DDAVP (Desmopressin)	0.4 μg/kg IV	Promotes platelet adherence. Consider for bleeding with platelet inhibitor use along with platelet transfusion.

U, unit; *μg/kg IV*, micrograms per kilogram intravenously.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Three Airway Management Techniques for Airway Decontamination in Massive Emesis: A Manikin Study

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Section Editor: John Ashurst, DO
Submission history: Submitted January 8, 2019; Revision received June 17, 2019; Accepted June 29, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.6.42222

Introduction: Emesis occurs during airway management and results in pulmonary aspiration at rates of 0.01% – 0.11% in fasted patients undergoing general anesthesia and 0% - 22% in non-fasted emergency department patients. Suction-assisted laryngoscopy and airway decontamination (SALAD) involves maneuvering a suction catheter into the hypopharynx, while performing laryngoscopy and endotracheal intubation. Intentional esophageal intubation (IEI) involves blindly intubating the esophagus to control emesis before endotracheal intubation. Both are previously described techniques for endotracheal intubation in the setting of massive emesis. This study compares the SALAD and IEI techniques with the traditional approach of ad hoc, rigid suction catheter airway decontamination and endotracheal intubation in the setting of massive simulated emesis.

Methods: Senior anesthesiology and emergency medicine (EM) residents were randomized into three trial arms: the traditional, IEI, or SALAD. Each resident watched an instructional video on the assigned technique, performed the technique on a manikin, and completed the trial simulation with the SALAD simulation manikin. The primary trial outcome was aspirate volume collected in the manikin's lower airway. Secondary outcomes included successful intubation, intubation attempts, and time to successful intubation. We also collected pre- and post-simulation demographics and confidence questionnaire data.

Results: Thirty-one residents (21 anesthesiology and 10 EM residents) were randomized. Baseline group characteristics were similar. The mean aspirate volumes collected in the lower airway (standard deviation [SD]) in the traditional, IEI, and SALAD arms were 72 (45) milliliters per liter (mL), 100 (45) mL, and 83 (42) mL, respectively ($p = 0.392$). Intubation success was 100% in all groups. Times (SD) to successful intubation in the traditional, IEI, and SALAD groups were 1.69 (1.31) minutes, 1.74 (1.09) minutes, and 1.74 (0.93) minutes, respectively ($p = 0.805$). Overall, residents reported increased confidence (1.0 [0.0-1.0]; $P = 0.002$) and skill (1.0 [0.0-1.0]; $P < 0.001$) in airway management after completion of the study.

Conclusion: The intubation techniques provided similar performance results in our study, suggesting any one of the three can be employed in the setting of massive emesis; although this conclusion deserves further study. Residents reported increased confidence and skill in airway management following the experience, suggesting use of the manikin provides a learning impact. [West J Emerg Med. 2019;20(5)784-790.]

INTRODUCTION

Emesis during airway management is a common event. When it occurs, massive emesis is a major problem as resultant aspiration is associated with both morbidity and mortality.[1] In the operating room, approximately 0.01% – 0.11% will suffer some complication due to aspiration.[2] In the emergency department (ED), aspiration rates associated with rapid sequence intubation have been reported from 0% – 22%.[3] Current guidelines recommend risk assessment and prophylaxis as the basis for aspiration prevention.[4] Regardless, aspiration events still occur, and operators should be trained in the management of the patient who experiences massive emesis during airway management to mitigate the risk of profound airway contamination and aspiration.

Various techniques and devices have been developed for the management of massive emesis events. One such example is that of a suction laryngoscope studied by Mitterlechner et al.[5] In that investigation, the authors found a reduction in the number of esophageal intubations (EI) by inexperienced technicians when compared to a standard laryngoscope. However, due to the rarity of emesis events and ethical considerations, supporting evidence is limited. Thus, this is a research area of great need as pulmonary complications, such as pulmonary pneumonitis and pneumonia, lead to patient morbidity. A consensus exists that a pH less than 2.5 and a volume of pulmonary aspirate of greater than 0.3 milliliters per kilogram (mL/kg) is necessary for the development of pulmonary complications.[6] Patients undergoing emergency airway management who experience massive emesis are likely at risk of meeting these requirements.

Traditionally, the management of massive emesis during intubation includes first positioning the patient in a head-down position, followed by decontamination of the patient's airway by suctioning, then intubating using either direct laryngoscopy (DL) or video laryngoscopy (VL). Two other techniques have been discussed to manage such an event: suction-assisted laryngoscopy and airway decontamination (SALAD), and intentional esophageal intubation (IEI).[7-9]

The SALAD technique, previously described by Ducanto et al.[7], involves oral airway decontamination while simultaneously preserving VL views for intubation. At the onset of a massive emesis event, the operator clears the airway of vomitus to allow placement of video laryngoscope. With the suction catheter in the right hand and the laryngoscope in the left, the operator advances the suction catheter as a tongue depressor, suctioning vomitus, and allowing for advancement of the laryngoscope. Once a view of the glottis is observed, the operator maneuvers the suction catheter around the laryngoscope blade and uses his or her left hand to hold it in place, thereby freeing the right hand for placement of the endotracheal tube (ETT).

The IEI technique, previously described by Sorour et al.,[9] involves intentionally intubating the esophagus to achieve control of massive emesis, oral cavity decontamination, and endotracheal intubation. At the onset of a massive emesis event, the operator blindly places the ETT. After the ETT is placed and the cuff is inflated, if the tube is placed in the esophagus the hope is that vomitus is controlled by shunting it away from the patient via the ETT. This then allows for the oropharynx decontamination and endotracheal intubation.

Population Health Research Capsule

What do we already know about this issue?
Emesis during airway management is common, particularly in the emergency department, and can result in serious morbidity and mortality.

What was the research question?
This study compared the effectiveness of three intubation techniques using a massive emesis manikin model.

What was the major finding of the study?
The intubation techniques performed similarly, suggesting any of the three techniques can be used during massive emesis.

How does this improve population health?
This is the first study to investigate intubation technique effectiveness during massive aspiration and will likely spur future research to improve patient care.

However, no data exists comparing the effectiveness of either of these techniques because studying these techniques in human trials would be particularly challenging and a suitable animal model does not exist. Recently, a traditional airway-training manikin was modified that provides a realistic model of massive emesis or upper gastrointestinal hemorrhage during airway management.[7,10] The SALAD simulation manikin[7,10] consists of a standard airway-training manikin with vinyl tubing attached to the manikin's esophageal port connected to a self-priming, drill-powered fluid pump. The fluid pump is connected to a container filled with a mixture of aspirate (vinegar and xanthum gum). When the fluid pump is activated, aspirate is pumped into the oral cavity of the manikin. The aspirate flow rate to the manikin is adjustable by the operator. The exact SALAD simulation manikin build used during this trial was similar to the original build described by DuCanto et al. except for the modification of using a 1/10 horsepower submersible utility pump (Ace Hardware, Oak Brook, Il) instead of a drill-driven pump.

The objective of this pilot study was to compare the effectiveness of three different airway management techniques (traditional, IEI, and SALAD) for airway decontamination and tracheal intubation in the setting of a simulated massive

emesis with resultant airway contamination. Secondarily, we explored the perceived learning impact of using the SALAD simulation manikin.

METHODS

This study is a single-center, open-label, randomized controlled trial conducted at the University of Wisconsin Hospitals and Clinics (UWHC). The University of Wisconsin School of Medicine and Public Health (UWSMPH) institutional review board approved this study, and informed written consent was obtained from all study subjects.

Senior anesthesiology and emergency medicine (EM) residents, affiliated with the UWSMPH were invited to participate in the trial. Residents were eligible if they were in either the anesthesiology or EM residency programs in their postgraduate year (PGY) 2, 3 or 4 (Figure 1). The EM residency program affiliated with the UWSMPH is a three-year training program. Participants were block randomized on the basis of specialty training (anesthesia or EM) to one of the three trial arms: traditional, IEI, or SALAD using a random number generator. Before beginning the study, each subject completed a pre-simulation questionnaire, which included demographic questions, level of confidence and skill in airway management during massive emesis, experience handling massive emesis during airway management, and prior experience using simulation to learn airway management skills. On study completion, the residents completed a post-simulation questionnaire regarding their level of confidence and skill in airway management during massive emesis, plan to apply their trained technique, perceived usefulness of the training session, and perceived usefulness of the training simulator.

At study onset, each subject watched a five-minute video demonstrating his or her assigned airway decontamination study technique. Subjects then practiced the technique on a manikin of similar make that had not been modified to vomit. Three successful intubations using the assigned technique were required before the subject could proceed to the simulation.

Once the technique familiarization session was complete, the subject was brought to the study manikin and informed that the patient needed to be intubated using the airway decontamination technique they had just practiced. All subjects were provided with GlideScope (Verathon Inc., Bothell, WA) video laryngoscope and a standard Yankauer suction catheter. The simulation began when vomit was visualized in the manikin's posterior oropharynx. The simulation ended with successful placement of the endotracheal tube as indicated by air movement in the manikin's lungs.

The examiner recorded the time with a stopwatch. A beaker was placed in-line with the right mainstem bronchus of the manikin to collect fluid entering the lungs (Figure 2). The beaker was weighed before and after the examination. The difference was recorded as the volume of aspirate that had entered the lungs. The suction canister was also weighed before and after examination to determine the volume of simulated vomit suctioned by the subject.

The primary study outcome was the compared volume of fluid collected from the lungs between the study arms. To detect a true difference of 25 mL with a variance of 20 mL, a sample size of 12 subjects was required in each arm (alpha = 0.05, beta = 0.80). Secondary study outcomes included successful intubation, time to successful intubation, and the number of intubation attempts for successful intubation. In addition, we collected pre-simulation and post-simulation questionnaire data regarding

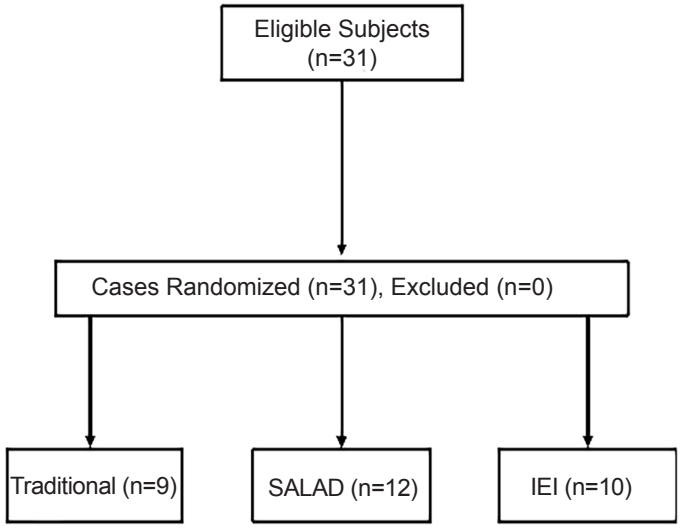

Figure 1. CONSORT diagram.
SALAD, Suction Assisted Laryngoscopy Airway Decontamination; *IEI,* intentional esophageal intubation.

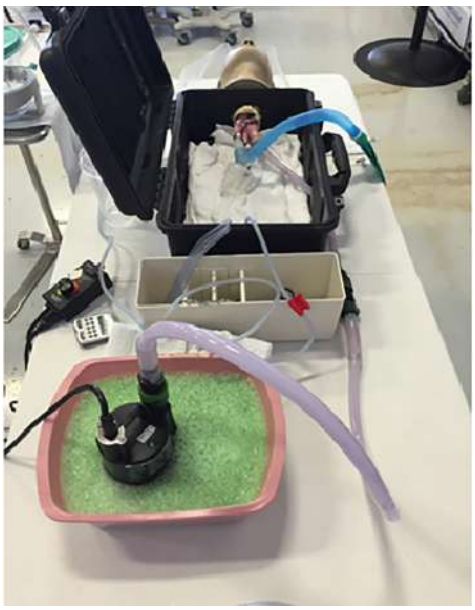

Figure 2. Experimental Setup.

the training aspects to further investigate the manikin system as a teaching tool. A priori subgroup analysis was performed between PGY status and residents who had vs had not managed the airway of a patient with massive emesis.

We summarized all data by mean (SD), median (IQR), or frequency (%). Demographic and outcome data were compared between randomized treatment methods with analysis of variance or chi-square tests. Post-hoc pairwise comparisons used Holm adjustments to keep a family-wise error rate of 5%. Secondary analyses of outcome measures included grouping subjects by previous experience with patients who have had a massive emesis during airway management, as well as PGY status. These analyses are considered exploratory, and therefore no adjustment for multiple testing over the same outcome measures was done. We conducted similar analyses for the survey questions to assess for differences between groups in confidence and knowledge of management techniques. All tests were conducted at a 0.05 significance level and all analyses were conducted using R version 3.1.1 (Free Software Foundation Inc., Boston, MA).

RESULTS

After inviting all available anesthesiology and EM residents, 31 residents (21 anesthesiology and 10 EM residents) consented and participated in the study. There were no significant differences in randomization between the three trial arms in terms of age or PGY level (Table 1). The mean (SD) volume of aspirate collected in the lower airway was higher for the IEI and SALAD methods (traditional 72 (45) ml; IEI 100 (45) ml; SALAD 83 (42) ml), but the differences did not reach statistical significance (p = 0.392) (Table 2). Additionally, time to successful intubation was similar between the three groups (traditional 1.69 (1.31) minutes; IEI 1.74 (1.09) minutes; SALAD 1.74 (0.93) minutes; p = 0.805).

Subgroup analysis of residents who had vs had not previously managed massive emesis in a patient during airway management found no difference in mean volume in lungs (82 [48] ml vs 88 [40] ml; p = 0.716) or time to successful intubation (1.71 [1.20] minutes vs 1.74 [0.9] minutes; p = 0.79). PGY-2 residents had higher mean volume in lungs (PGY-2 106 [36] ml; PGY-3 63 [49], PGY-4 91 [38]; p = 0.084) and longer times to successful intubation (PGY2 1.68 [0.71] minutes, PGY-3 1.39 [0.46] minutes, PGY-4 2.10 [1.58] minutes; p = 0.674), when compared to PGY-3 and PGY-4 residents, but these differences did not reach statistical significance (Table 3).

On the pre-simulation questionnaire, PGY-2 residents reported lower confidence ratings (median (IQR)) in managing massive emesis during airway management compared to PGY-3 and PGY-4 residents (PGY-2 3.0 [2.0 - 3.0], PGY-3 3.0 [3.0 - 3.0], PGY-4 3.0 [3.0 - 3.0]; p = 0.046) (Table 4). On a post-simulation questionnaire, residents overall reported a statistically significant increase in confidence ratings in airway management

Table 1. Baseline Characteristics.

	IEI (n=10)	SALAD (n=12)	Traditional (n=9)	p-value
Sex, Female	2 (20.0%)	2 (16.7%)	5 (55.6%)	0.169
Resident				0.8
CA	6 (60.0%)	8 (66.7%)	7 (77.8%)	
EM	4 (40.0%)	4 (33.3%)	2 (22.2%)	
Age	31.9 (7.2)	30.2 (2.5)	29.7 (2.3)	0.526
PGY				0.241
2	5 (50.0%)	3 (25.0%)	1 (11.1%)	
3	1 (10.0%)	5 (41.7%)	5 (55.6%)	
4	4 (40.0%)	4 (33.3%)	3 (33.3%)	

Data are mean ± standard deviation or number and percent.
CA, clinical anesthesia; *EM,* emergency medicine; *PGY,* post graduate year; *SALAD*, Suction Assisted Laryngoscopy Airway Decontamination; *IEI,* intentional esophageal intubation.

Table 2. Primary and Secondary Outcomes of Airway Management Technique.

	IEI (n=10)	SALAD (n=12)	Traditional (n=9)	p-value
Volume in lungs (mL)	100 (45)	83 (42)	72 (45)	0.392
Successful intubation	10 (100.0%)	12 (100.0%)	9 (100.0%)	1
Time to intubate (min)*	1.74 (1.09)	1.74 (0.93)	1.69 (1.31)	0.805
Intubation attempts	1.56 (1.29)	1.45 (1.17)	1.5 (1.28)	0.85

Reported as mean (SD).
*p-value from test based on log transformed data.
SALAD, Suction Assisted Laryngoscopy Airway Decontamination; *IEI,* intentional esophageal intubation.

skills and skill in airway suction techniques after completing the study (1.0 [0.0-1.0], p = 0.002; 1.0 [0.0-1.0], p < 0.001). However, PGY-2 and PGY-3 residents thought the training was more useful compared to PGY-4 residents (PGY-2 5.0 [4.0 - 5.0]; PGY-3 5.0 [4.0 - 5.0]; PGY-4 4.0 [3.5 - 4.0]; p = 0.018) and planned on applying the trained technique (PGY-2 4.0 [4.0 - 5.0]; PGY-3 4.0 [4.0 - 5.0]; PGY-4 4.0 [3.5 - 4.0]; p = 0.014).

DISCUSSION

The main conclusion from our study is that the three intubation techniques provided similar performance results, suggesting any of the three techniques can be employed in the setting of massive emesis. However, the traditional method of intubation during massive emesis, while statistically similar, tended to outperform IEI and SALAD in controlling aspirate volume in the lower airway. To explore the trend, but lack of statistical significance further, given the smaller-than-planned sample size for our study (see Limitations section below), we assessed the effect size of the volume aspirate data by looking at eta squared. The result (0.069) indicates that group designation accounted for 6.9% of the variability in the outcome, which according to Cohen et al.[11] guidelines, suggests there is at least a medium effect of group designation on lower airway aspirate volume, and that the study's small sample size is the reason for the non-significant statistical test. Similarly, the results for time to successful intubation followed an analogous pattern (traditional 1.69 minutes [1.31] vs IEI 1.74 minutes [1.09] vs SALAD 1.45 minutes [1.17]; p = 0.805).

The SALAD simulation manikin proved an effective simulator and airway management trainer. The simulator, developed and studied by DuCanto et al., was found to improve the reported overall airway management confidence in a diverse group of learners.[7] Similarly, we demonstrated that the SALAD simulator manikin is a useful teaching tool. EM and anesthesia residents across different levels of training reported a statistically significant increase in confidence ratings in overall airway management skills and skill in airway suction techniques before and after our simulation (1.0 [0.0-1.0], p = 0.002; 1.0 [0.0-1.0], p < 0.001). Based on our survey results and the study conducted by DuCanto et al., the SALAD simulation manikin has utility as a teaching tool for intubators of all levels in different specialties.

Simulation is fast becoming a popular and effective tool to improve health professional education. Cook et al.[12] found that in comparison to no intervention, technology-enhanced simulation has had positive effects on "outcomes of knowledge, skills, and behaviors and moderate effects for patient-related outcomes." Therefore, simulation-based airway management training would likely help health professionals because of the rarity with which emergencies requiring special techniques occur. This idea is supported by Kennedy et al.,[13] whose group provided evidence that a simulation-based airway management curriculum was more effective in comparison to no simulation interventions, and that simulation was associated with a higher learner satisfaction.

Of note, PGY-4 residents using the SALAD simulation manikin indicated they did not plan on applying the trained technique as much as the junior residents. We suspect that PGY-4s, being farther along in their career, are less impressionable than the PGY-2s and PGY-3s. Additionally, PGY-4s may be more familiar with a specific technique of airway decontamination and less willing to explore new techniques. PGY-2 and PGY-3 residents, still working to build foundational experiences, are more open to developing new airway management techniques. Thus, incorporating training with the manikin earlier in a resident's career will perhaps have a more significant influence on the development of a resident's airway management preferences.

LIMITATIONS

Several limitations existed in our study. The first, and most significant, was the failure to enroll an adequate number of residents to fulfill the power requirement. This resulted from a relative few number of eligible residents at our institution combined with a relative lack of interest. As discussed above, this impacted the statistical test result (ie, a failure to reach statistical significance for observed differences), while our exploration of the effect size suggests at least a medium effect associated with group assignment on the primary study outcome. Therefore, it is reasonable to believe the observed differences in the primary study outcome between the study groups are true, and this deserves further study in a larger investigation.

Second, the simulator itself may have influenced the results of the study. The simulator has a stiff supraglottic area, allowing the residents to easily insert the laryngoscope blade and quickly

Table 3. PGY Subgroup Analysis of Primary and Secondary Outcomes.

	PGY 2 (n=9)	PGY 3 (n=11)	PGY 4 (n=11)	p-value
Volume in lungs (mL)	106 (36)	63 (49)	91 (38)	0.084
Successful intubation	9 (100.0%)	11 (100.0%)	11 (100.0%)	1
Time to intubate (min)*	1.68 (0.71)	1.39 (0.46)	2.10 (1.58)	0.674
Intubation attempts	1.48 (1.21)	1.41 (1.18)	1.5 (1.28)	0.315

Reported as mean (standard deviation).
*p-value from test based on log transformed data.
PGY, post graduate year; *mL*, milliliters; *min*, minutes.

Table 4. Survey Analysis Based Off PGY Status.

	PGY 2 (n=9)	PGY 3 (n=11)	PGY 4 (n=11)	p-value
Pre-training				
Confidence in airway management	3 (2 - 3)	3 (3 - 3)	3 (3 - 3)	0.046
Skill in airway suction techniques	3 (2 -3)	3 (2 - 3)	3 (3 - 3)	0.099
Post-training				
Confidence in managing vomiting case	3 (3 - 4)	3 (3 - 4)	4 (3 - 4)	0.387
Skilled with various suction techniques	3 (3 - 4)	3 (3 - 4)	4 (4 - 4)	0.497
Plan to apply trained technique	4 (4 - 5)	4 (4 - 5)	4 (4 - 4)	0.014
Was training useful	5 (4 - 5)	5 (4 - 5)	4 (4 - 4)	0.018
Simulator realistic to challenge skills	4 (4 - 5)	4 (4 - 5)	4 (4 - 4)	0.425

Data are median (interquartile range).
PGY, post graduate year.

view the vocal cords. In clinical practice, the resident would likely be more careful and systematically insert the laryngoscope blade. Slower insertion of the laryngoscope blade would allow for more volume to fill the hypopharynx and lungs. Thus, the stiffness of the simulator could have decreased the mean volume of aspirate in lungs and time to successful intubation of the traditional and SALAD techniques.

Next, the consistency of the simulated vomit could have impacted the study. Due to our pumping system, we were unable to provide a "chunkiness" to the simulated vomit that would simulate half-digested, recently-chewed food. These food particles act as obstacles to operators intubating patients and could have provided a realistic challenge in determining the effectiveness of the techniques. For example, IEI could be less hampered by the food items aspirated because there is less reliance on commonly used, rigid suction catheters that are often obstructed by such particles.

Lastly, due to variation in the day-to-day viscosity of the simulated vomit, some residents experienced a slightly different simulation. While a servomotor was used to control flow rate and tests were run to ensure the consistency of the flow rate, slight differences were anecdotally experienced between the trial runs. Had the pump run faster for one of the specific techniques, this could have impacted the performance results.

CONCLUSION

This is the first study to attempt to assess the efficacy of different methods available for managing massive emesis during airway management. Our findings suggest the three tested methods provide similar results in our simulated model. A larger study with more power or additional operator training in the novel methods (ie, IEI and SALAD) is needed to determine more definitive results. Our study subjects reported the modified airway manikin provides reasonably realistic simulation for managing massive emesis or upper gastrointestinal hemorrhage and may also be useful as a simulator for airway management. Survey results suggest training with the manikin may impart a learning effect.

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Conflicts of Interest: By the WestJEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. Funding was provided by the Department of Anesthesiology at the University of Wisconsin, the Anna K. Arndt Professorship in Anesthesiology, and the Foundation for Anesthesia Education and Research.

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Undocumented Patients in the Emergency Department: Challenges and Opportunities

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Section Editor: Tony Zitek, MD
Submission history: Submitted October 30, 2018; Revision received June 17, 2019; Accepted July 1, 2019
Electronically published August 12, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.41489

In the United States, undocumented residents face unique barriers to healthcare access that render them disproportionately dependent on the emergency department (ED) for care. Consequently, ED providers are integral to the health of this vulnerable population. Yet special considerations, both clinical and social, generally fall outside the purview of the emergency medicine curriculum. This paper serves as a primer on caring for undocumented patients in the ED, includes a conceptual framework for immigration as a social determinant of health, reviews unique clinical considerations, and finally suggests a blueprint for immigration-informed emergency care. [West J Emerg Med. 2019;20(5)791-798.]

INTRODUCTION

Ms. G.S. is a 35-year-old woman presenting with "migraines." She sits, tearful, clutching her head with both hands as she hunches over the foot of her bed. As the providers enter the room, her friend whispers, "She's been under a lot of stress." The patient explains that she is a single mother of three children working as a housekeeper. Work has been hard to find this month, and her client refused to pay her after she worked all day. After asking why she didn't go to the police, she reveals that she is undocumented. Without the payment she was supposed to receive today, she cannot pay her rent and faces eviction. Her head has been hurting for weeks, but she has no health insurance and does not have a primary care provider. Her friend convinced her to come to the emergency department (ED) but she doesn't want to incur another bill, so she would prefer to leave.

The case of Ms. G.S. illustrates some of the many barriers that our undocumented patients face in achieving medical and social well-being. More than 11.3 million undocumented people currently reside throughout the United States.[1] Among this population, 47% are women and approximately 9% are minors. The majority of undocumented individuals are from Mexico (56%), followed by Central America (15%), and Asia (14%).[1] Nationally, the Hispanic undocumented population comprises 4% of the entire population but 4.8% of the workforce.[2] Undocumented individuals have high rates of structural vulnerability compared to documented immigrants and are more likely to live below the federal poverty level (56% vs 32%). Also, compared to documented immigrants, more undocumented immigrants have not completed high school (52% vs 43%), and have poor English literacy (75% vs 53%). Almost 7% of all U.S. K-12 students have at least one parent who is undocumented, and one third of children of undocumented parents live in poverty.[3]

The aim of the Patient Protection and Affordable Care Act (PPACA), signed into law March 23, 2010, was to decrease the number of uninsured Americans through the expansion of public and private health insurance. The bill explicitly excluded undocumented residents in the U.S.[4] Prior to the passage of the PPACA, it was estimated that undocumented residents made up 20% of the 46 million

uninsured Americans.[5] With the passage of the PPACA, few undocumented individuals gained eligibility for direct enrollment into health plans, although coverage improved slightly through funding of Federally Qualified Health Centers and employer-based coverage. Consequently, more than 45% of non-elderly undocumented immigrants are uninsured. As of 2017, non-citizen U.S. residents, including undocumented individuals and legal permanent residents, make up 7% of the U.S. population but approximately one quarter of the U.S. uninsured population.When healthcare is accessed, undocumented individuals report lower quality of health services including fewer doctor visits, lower rates of preventative testing, and lower perceived quality of care relative to U.S.-born Latinxs.[6] Inequities in care may be compounded by language barriers in the setting of inadequate access to and utilization of interpreter services.[7] Current federal immigration regulations risk exacerbating non-citizen reliance on ED care through increased barriers to alternative venues.[8]

Barriers to routine care increase dependence on public institutions and EDs. In California, 39% of undocumented individuals lack a usual source of healthcare other than the ED. They are also less likely to have had an ED visit over the preceding year compared to naturalized and U.S.-born citizens.[3,9,10] Cost is often a point of contention in debates over healthcare for the undocumented.[11] While robust and up-to-date statistics regarding healthcare utilization by undocumented individuals is limited, existing data strongly suggests that undocumented residents have lower per-capita healthcare expenditure than U.S. citizens. Furthermore, the undocumented population contributes to, but is ineligible to access, the Medicare Trust Fund, resulting in a large surplus of funds to this public healthcare-funding mechanism.[12]

Therefore, despite lower rates of healthcare utilization and expenditures compared to U.S. citizens, undocumented U.S. residents remain uniquely dependent on the ED for care. It is essential for emergency medicine (EM) providers to understand the unique health challenges and barriers to healthcare access faced by this population.

Immigration as a Social Determinant of Health

"The social determinants of health are the conditions in which people are born, grow, live, work and age. These circumstances are shaped by the distribution of money, power and resources at global, national and local levels."[13]Immigration and undocumented legal status are important but often overlooked social determinants of health. Like other social determinants of health, immigration status both directly and indirectly impacts health and healthcare access. Some examples of the direct health effects of one's legal status include unsafe work and living conditions, fear of detention and deportation, migration-related trauma, and barriers to accessing health-care. Undocumented status indirectly impacts health by limiting access to public service benefits, housing, preventative health screening, and other health promoting services.[14] Yet among other social determinants of health, undocumented status is unique in that it is overtly criminalized and persecuted. Heightened criminalization of those without legal status, and their families, serves to compound the aforementioned barriers.

Further, the effects of anti-immigrant legislation and a culture of fear and distrust on healthcare utilization are well documented.[15] Total well visits decrease, while acuity increases across a spectrum of contexts including psychiatric visits in California, pediatric ED visits in Georgia, or prenatal and well-child visits in Arizona.[16-18] One in eight undocumented Latinx immigrants fears discovery and deportation when using the ED, which explains some of the sentiments fueling the pattern.[19]

Clinical Considerations in Caring for Undocumented Patients in the Emergency Department

There are several unique considerations to caring for undocumented patients in the ED. The following six cases provide examples and analysis of some of these unique situations.

Case 1

Mr. E.B. is a 48-year-old man with a history of end stage renal disease on dialysis. He has suffered two cardiac arrests secondary to delayed dialysis and relies solely on the ED for his dialysis sessions. He is asymptomatic today but is afraid he will not be able to secure transportation to return to the ED before suffering another complication from delayed dialysis. He presents to the ED hoping to talk to social work about transportation for tomorrow's dialysis session.

Because they are ineligible for Medicare and Medicaid, undocumented residents are ineligible for routine dialysis. These individuals often rely on emergency dialysis in EDs funded through states' emergency Medicaid funds. Dependence on emergency care services for a life-sustaining therapy creates significant medical and psychological distress for patients and their families and is associated with increased mortality.[20,21] Compared to scheduled outpatient provision of this life-sustaining therapy, ED dialysis is 3.5 times as costly. Furthermore, lack of access to routine dialysis increases utilization of scarce emergency medical resources and results in lost work productivity for patients.[22] Based on the negative medical, psychological and financial implications of existing practices, providers should advocate locally and nationally to ensure routine scheduled dialysis for all patients regardless of citizenship status.

Case 2

Ms. J.G. is an 18-year-old female brought in by family for an acute acetaminophen ingestion secondary to suicidal ideation. She is in fulminant hepatic failure.

She needs transfer to a transplant center to be evaluated for emergent liver transplant. One by one, you contact the local transplant centers. Each time the transplant surgeon accepts, but the transfer center states the request is on hold until it can "look further into funding options." You then learn that she is undocumented.

Lack of documentation status can exclude a patient from receiving an organ transplant. Although the United Network for Organ Sharing (UNOS) does not exclude patients based on citizenship status specifically, lack of health insurance precludes undocumented immigrants from being listed for organ transplantation.[23] Few patients without health insurance are ever listed. Given the barriers to health insurance faced by non-citizens, undocumented patients are effectively excluded from consideration for transplant.[24] Despite this, 3% of all organ donors in the U.S. are undocumented and most of their organs are transplanted into U.S. citizens.[25] In an ethical analysis of this point, Wightman et al. write, "Any system that uses the organs of individuals who would themselves not be considered eligible for a transplant because of inability to pay is clearly unjust."[26] Economic analysis has demonstrated that the "break-even" point after which kidney transplantation is cheaper than ongoing dialysis is only 1.5-2.7 years.[27] In addition, undocumented patients with Medicaid have post-transplant outcomes equal to that of U.S. citizens on Medicaid, refuting the argument that patients with limited financial resources are not able to adequately maintain their health post-transplant.[28] In 2015, Illinois became the first state to use state funding to cover kidney transplantation costs for undocumented residents.[28]

Case 3

Mr. S.F. is an 18-year-old male presenting the ED after he was assaulted while walking home from work. This is the second time he has been assaulted and is concerned for his safety. When asked if he'd like to file a police report he declines, fearing discovery of his immigration status.

Undocumented groups are at risk for violent injury and reinjury because they are less likely to engage with law enforcement. Fear may prevent victims of violence from reporting crime or seeking other forms of support. Fear of deportation may be exploited to perpetuate both domestic violence and violence in the workplace in the form of human trafficking and/or unsafe or illegal work conditions. Recognizing this vulnerability, the federal government created the U-Visa as a part of the "Victims of Trafficking and Violence Protection Act of 2000,"[29] which offers a path to legal residency to those who are willing to support law enforcement in the prosecution of the crime.

In cases where a patient's citizenship status hinders communication and care, the emergency provider may consider articulating the confidentiality of the patient-doctor encounter, offering an introductory explanation of a U-Visa, and referral to either social work or appropriate local legal aid agencies. This intervention alone may reduce the likelihood of future victimization and offer the victim channels of support in an otherwise alienating environment.

Case 4

Mr. J.S. is 39-year-old man who presents after a syncopal episode while working in the fields in the heat. He had been feeling lightheaded all day. After receiving intravenous fluids, he improves. His employer remains at bedside throughout her medical care, repeatedly interjecting into the conversation, and is reluctant to leave the room. When asked more pointedly, the employer steps out of the room and the patient divulges that his worksite does not allow water breaks. When asked if he wants to report this to local authorities, he states he was brought to the U.S. to work and is afraid of being fired and deported.

Like Mr. J.S., 12 million people live in conditions of coerced labor or sexual servitude generating over 150 billion dollars in profit.[30] Between 600,000-800,000 people are trafficked across borders globally, almost half under the age of 18 and the majority female. Between 14,000-50,000 people are trafficked into the U.S. every year. Undocumented migrants are disproportionately represented in the trafficked population and have higher barriers to safety than U.S.-born victims, including poor social support and fear of deportation. Many labor-trafficking victims (67%) and a large percentage of sex-trafficking victims (13%) are believed to be undocumented.[30] Considering the barriers to healthcare for undocumented individuals, the ED visit represents an opportunity to identify and assist undocumented victims of trafficking.[31,32]

The identification of trafficking victims is obstructed by a multitude of factors including distrust of authority, fear of retaliation, and fear of deportation.[33] When concerned, providers should seek to interview patients independently, build trust, and offer resources that may be used later if and when the victim feels comfortable seeking assistance. Specifically, providers may inform possible victims of the T-Visa program. Like the U-Visa, the T-visa offers temporary and possibly permanent visas to victims of trafficking who agree to assist law enforcement in the identification of traffickers.

Case 5

Mr. J.F. is a 35-year-old man presenting with recurrent headaches since immigrating to the U.S. from El Salvador. He and his brother owned a tire repair business, which he left behind after his brother was killed because they couldn't comply with increasing extortion demands from a local gang. He endorses frequent panic

attacks and flashbacks, and fears deportation back to his community where his family members continue to receive threats.

Emergency providers may encounter individuals or families who are undocumented and facing or fleeing torture in their home country. Many recent migrants from Central America and Mexico cite the burden of gang violence, political violence, and torture as reasons for fleeing their home countries. A survey of migrants by Médecins Sans Frontiers found that over half of migrants reported violence as the primary driver of emigration while 68.3% endorsed being victims of violence en route.[34] Past exposure to political violence may manifest clinically as depression, post-traumatic stress disorder, panic disorders, chronic pain, and impaired physical functioning.[29,34] Despite the high levels of torture and violence in Mexico and Central America, few submit asylum applications.[35] ED providers should consider the burden of torture and political violence in clinical encounters and consider referral to trusted legal aid groups to seek asylum, programs for torture victims, and psychosocial support services.

Case 6

Ms. R.Z. is a 22-year-old woman brought in by U.S. Border Patrol officers who found her in the desert after she crossed from Mexico. She is hypothermic on initial examination. Her pregnancy test is positive. On further discussion she endorses sexual violence during her migration, inflicted by the smuggler she had paid to guide her from Guatemala.

While the total number of individuals successfully crossing the U.S. border is unknown, the number of apprehensions at the U.S. border was approximately 415,000 in 2016.[36] The vast majority occur at the southern border and are of individuals from Mexico or Central America. The factors that underlie the ebb and flow of migration rates are complex, including international disparities in wealth, violence, and border militarization. Increased expenditures on border militarization have led to more perilous journeys for migrants.[37] Prior to 1994, border-crossing deaths were a rare occurrence. Progressive militarization of the border pushes migrants to pursue more treacherous routes, exposing them to extremes of hot and cold.[38] Common causes of death and morbidity include drowning, dehydration, motor vehicle accidents, and violence from law enforcement.

According to U.S. federal statistics, 307 immigrants died during border crossings in 2014 alone and over 6,000 have died since 1998. The Mexican government, however, estimates nearly triple that of the U.S. government.[37] The health risks of migration begin long before the hazardous U.S. border crossing. Despite being guaranteed "a right to receive healthcare provided by either the public or private sector, regardless of their migratory status" by the Mexican Migrant Law, most migrants from Central America travel long distances across Mexico without access to medical care. Interviews with migrant women at Mexico's southern border found that 28% had transactional sex, 8.3% had been sexually assaulted, and 9.2% had suffered sexual harassment.[39] As many as six in ten women may be sexually assaulted at some time during their trip.[40]

Creating an Immigration-Informed Emergency Department

"…[T]he ED is singled out as the only component of the medical system and, in this case, *the only component of the entire social welfare system*, that is protected by law for many of the most disadvantaged."[41]

In the face of daunting political, social, and economic forces that threaten the health of undocumented populations, there are tangible steps ED providers may take to promote health equity. Here we offer a blueprint for creating an immigration-informed ED (Figure). Improving the care and health of undocumented populations begins by training providers that immigration status is a modifiable social determinant of health. Trainees in EM along with other hospital staff should be encouraged to reframe discussions on immigration status from a polarizing political topic to one that directly impacts patient care. Understanding the demographic composition of one's ED, hospital, and local community is vital. This provides a basis for understanding cultural and structural conditions that shape ED visits including perceptions of the healthcare system, traditional practices, and factors driving emigration from countries of origin.

Clear communication between patients and providers is critical to compassionate and equitable care for undocumented patient populations. To improve the quality, safety, and satisfaction of patient care – including developing trust and promoting treatment adherence – it is important to identify language barriers and use professional interpreters. This is not merely a formula for improved care but is also legally enshrined in Title VI of the 1964 Civil Rights Act of the Department of Health and Human Services, which states: "No person may be subjected to discrimination on the basis of national origin in health and human services programs because they have a primary language other than English."[42] Undocumented patients may be denied access to health promoting services and treatment modalities that are accessible to other patients, including public programs, nursing care, and particular medical therapies following discharge from the ED.[43] ED providers should work with social workers and community-based providers to provide tailored care plans.

Immigration relief is the adjustment of immigration status to a legal category that allows the person to stay in the U.S. without fear of deportation. Adjustment of

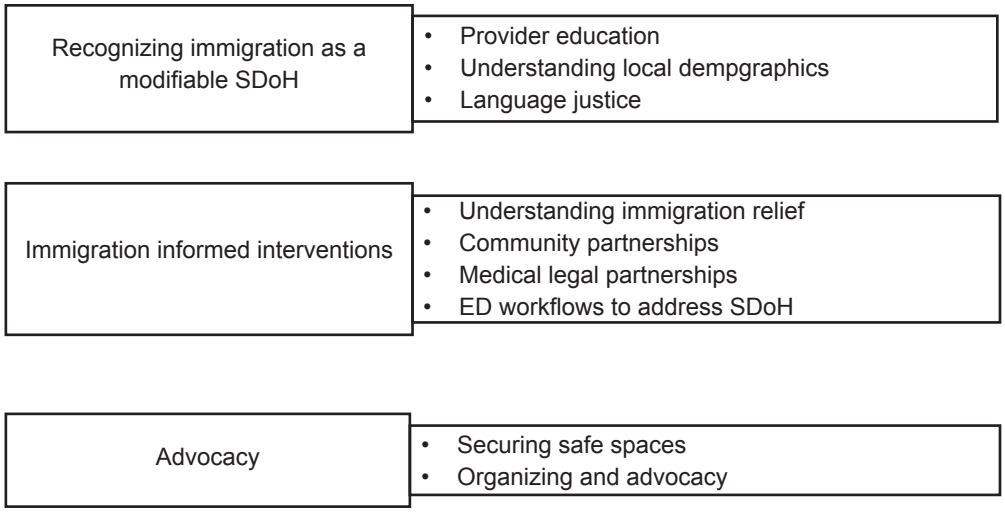

Figure 1. Components of an immigration-informed emergency department.
SDoH, social determinant of health; *ED,* emergency department.

legal status has multiple benefits that contribute to long-term improvement in health including stabilization of socioeconomic status and eligibility for health insurance (Table 1). Providers serving undocumented patients should be aware of the types of immigration relief most relevant to ED patient care (Table 2). Although the intricacies of immigration relief eligibility are beyond the purview of ED providers, understanding these basic categories will prompt particular attention to immigration status in specific patient populations and disease presentations. Providers should be aware that a multitude of barriers have been erected to limit asylum and immigration relief and take care not to promise immigration-status adjustment. Instead, cases should be referred to qualified legal advocates to avoid misinformation. Formation of medical-legal partnerships, as discussed below, can improve identification of eligible cases.

Strengthening ties with local, community-based organizations and medical legal partnerships can facilitate linking undocumented patients to social services. Community-based organizations understand challenges faced by undocumented groups, have organized resource databases, and may be able to facilitate successful completion of the intended discharge plan. Coordination with local legal aid groups may streamline referral for victims of trafficking, violence, and others that may qualify for legal status change or benefit from legal rights education. Vetting of community partners is imperative because of the high prevalence of predatory legal service providers.[44]

Given the vulnerability of this patient population, and impoverished communities more generally, safety-net facilities may consider building medical-legal partnerships to integrate legal services into the clinical space.[45] In addition to legal status adjustment, immigration legal providers may alleviate fear and anxiety by educating patients about their legal rights in the home, workplace, and public. The feasibility of these interventions may be limited by time constraints of ED providers. Providers may consider partnerships with social workers, community-based organizations, and local student volunteers to establish more robust systems of social screening, referral and case management out of the ED to facilitate referrals.[45]

By bearing witness to the human impact of anti-immigration legislation on patient health, ED providers make excellent advocates on the local and national level. Political policies enforcing the detention, criminalization and deportation of undocumented populations cause increased fear of entering the public sphere and fear of engaging with social services, including healthcare.[19,46] Consequently, undocumented populations are at increased risk of foregoing preventative and potentially life-saving medical care due to fear of detention. ED providers should advocate for policies that ensure sanctuary spaces for all patients, including those who are undocumented.[47] Central to this designation are hospital and health-system policies that support hospital staff in limiting cooperation with immigration agencies and agents. Sanctuary city and state policies such as those passed in California may offer guidance in policy creation, advocacy and implementation.[48] Beyond formal policies, hospitals and EDs should communicate their acceptance and support of undocumented communities through hospital signage, local community outreach, and partnership with local, community-based organization and trusted civil society groups.

Table 1. Benefits of obtaining legal immigrant status (immigration relief).

1.	Increaseding access to safe, legal employment, with increased opportunities for enrollment in employment-based health insurance.
2.	Improved socio-economic status with resultant stabilization of life situation.
3.	Possible eligibility for enrollment into federal or state programs for education or health services, i.e., Medicaid.
4.	Self-sufficiency and independence from exploitative living and work environments.

Existing political policies that limit access to health-promoting services and promote detention or criminalization are deleterious to the health of the undocumented patient population. For healthcare providers advocacy against the "illegality of humans" is inextricably intertwined with professional ethics and the principle of health as a fundamental human right. Emergency physicians, healthcare providers, and health systems striving for health equity should engage in local and national organizing to address these barriers to care, by advocating for paths toward legal status and funding to ensure equitable care such as routine dialysis and organ transplantation.

Offering a patient-centered lens to local organizing efforts, creating local immigration-focused provider groups, promoting the creation of sanctuary spaces, developing immigration-informed EDs, and formulating patient-centered position statements among professional organizations are just some of the avenues through which physicians may engage in advocacy to address immigration-related barriers to health. Inclusion of immigrant and undocumented communities in these organizing efforts is essential to ensure that advocacy efforts align with needs.

CONCLUSION

"*The physicians are the natural attorneys of the poor, and the social problems should largely be solved by them."*
Rudolf Virchow

The subject of citizenship and legality of populations is complex, contentious, and dynamic. It is clear that lack of citizenship negatively impacts access to healthcare and health. Similarly, the idea of "illegality of persons" contradicts the professional and societal obligations of healthcare providers. The cases highlighted here illustrate how existing systems fail to meet the needs of undocumented patients. We hope this primer informs clinicians in the ED about the multiple levels of barriers undocumented patients face and suggests potential provider- and system-level changes to counteract exclusionary policies and promote health equity. As is often the case, it falls upon healthcare providers to transcend existing norms to secure the medical and structural conditions requisite to the health of our patients.

ACKNOWLEDGEMENTS

We would like to thank Dr. Richelle Cooper, Dr. Jennifer Kasper, and Dr. Sam Dubal for their contributions and guidance in the preparation of this manuscript.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Table 2. Clinically relevant immigration-relief scenarios.

Immigration relief	Clinical scenario	Suggested phrasing
U-visa	Undocumented victims of certain serious crimes	I want to tell you that certain victims of serious crimes in the U.S. may qualify for immigration relief.
T-Visa	Survivors of human and labor trafficking	Some patients in your situation may be eligible for immigration relief and services.
Special Immigrant Juvenile Status (SIJS)	Undocumented patients under the age of 21 who have been abandoned, abused or neglected by one or both parents, including children in foster care, in guardianship proceedings, or on probation. Also includes those under 18 living with a single parent.	Some patients in your situation may be eligible for immigration relief. I wanted to tell you that if you qualify for immigration relief, it is important to talk to an immigration attorney as soon as possible.
Asylum and Convention against torture (CAT)	Undocumented patients who experienced persecution or torture in country of origin	Some patients who have suffered serious harm or threats of harm in their home country may be eligible for immigration relief.

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Potential of Mobile Health Technology to Reduce Health Disparities in Underserved Communities

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Section Editor: Mark I. Langdorf, MD, MHPE
Submission history: Submitted December 5, 2018; Revision received June 5, 2019; Accepted June 12, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.6.41911

Introduction: Mobile health (mHealth) has the potential to change how patients make healthcare decisions. We sought to determine the readiness to use mHealth technology in underserved communities.

Methods: We conducted a cross-sectional survey of patients presenting with low-acuity complaints to an urban emergency department (ED) with an underserved population. Patients over the age of two who presented with low-acuity complaints were included. We conducted structured interview with each patient or parent (for minors) about willingness to use mHealth tools for guidance. Analysis included descriptive statistics and univariate analysis based on age and gender.

Results: Of 560 patients included in the survey, 80% were adults, 64% female, and 90% Black. The mean age was 28 ± 9 years for adults and 9 ± 5 years for children. One-third of patients reported no primary care physician, and 55% reported no access to a nurse or clinician for medical advice. Adults were less likely to have access to phone consultation than parents of children (odds ratio [OR] 0.49, 95% confidence interval [CI], 0.32 – 0.74), as were males compared to females (OR 0.52, 95% CI, 0.37– 0.74). Most patients (96%) reported cellular internet access. Two-thirds of patients reported using online references. When asked how they would behave if an mHealth tool advised them that their current health problem was low risk, 69% of patients responded that they would seek care in an outpatient clinic instead of the ED (30%), stay home and not seek urgent medical care (28%), or use telehealth (11%).

Conclusion: In this urban community we found a large capacity and willingness to use mHealth technology in medical triage. [West J Emerg Med. 2019;20(5)799-803.]

INTRODUCTION

Minority and low-income patients have high levels of cell phone and mobile internet use.[1,2] Mobile health (mHealth) has the potential to enhance healthcare for underserved populations with limited access to traditional healthcare resources.[3] Emergency departments (ED) are increasingly being used as a safety net for underserved populations with health conditions that could be treated

in the primary care setting.[4] Development of high-quality mHealth tools to connect these underserved populations to medical advice could reduce ED utilization for low-acuity complaints. While the potential exists to decrease such disparities in healthcare access, the willingness of these patients to use mHealth is not well understood.[3] Hence, our goal was to determine healthcare access and readiness to engage with mHealth technology among patients using an urban ED for low-acuity complaints.

Population Health Research Capsule

What do we already know about this issue?
Mobile health (mHealth) technology has the potential to decrease ED visits and reduce cost in underserved communities.

What was the research question?
We sought to determine the readiness of patients in underserved communities to use mHealth technology.

What was the major finding of the study?
For medical triage, there is significant capacity and willingness to use mHealth technology.

How does this improve population health?
This study identifies mHealth as an avenue to help patients in underserved communities better align their medical problems with appropriate care.

METHODS

Study Design, Setting, and Selection of Participants

This study was a cross-sectional survey in an academic ED (>100,000 annual patient volume) with a large minority and low-income population. Enrollment occurred from June 2016 to January 2017 in Detroit, Michigan. At that time, the median income was $26,249 and 39.4% of the population was living below the federal poverty level. Patients were approached based on chief complaint. Research associates obtained informed consent from patients that met inclusion criteria. For children (<18 years), parents provided informed consent and completed the survey. Investigators also collected relevant clinical and demographic information from the electronic health record.

We included patients and parents of children presenting to the low-acuity section of the ED with chief complaints of sore throat, cough and congestion, non-traumatic headache, and symptoms of sexually transmitted infections. Exclusion criteria included patients <2 years and >50 years old, severe illness with expected hospital admission, and inability to provide informed consent.

Measures

The brief, 15-item, survey instrument focused on patient interest in mHealth and healthcare access (Appendix 1). We developed and refined items based on interviews with ED patients. Research associates administered surveys in person, and patients either completed a written paper form or verbally responded to survey questions based on their preference. We used REDCap electronic data capture tools to compile and code all survey data.

Outcomes and Data Analysis

The primary outcome was a descriptive assessment of healthcare access and engagement in mHealth technology. A formal sample size calculation was not performed. Analysis included descriptive statistics and univariate analysis with SAS 9.4 (Cary, NC). We used logistic regression to determine differences in mHealth use and engagement based on age and gender. We report odds ratios (OR) with 95% confidence intervals (CI). For the purpose of comparing age, we divided participants into millennials (birth year ≥ 1982) and non-millennials. The local institutional review board approved the study.

RESULTS

Characteristics of Study Subjects

A total of 560 patients participated in the study. Most of the patients were adults (449, 80%) and 360 (64%) were female. African Americans represented 496 (89%) of participants, Caucasians 29 (5%), and other races 35 (6%). The mean age was 28±9 years among adults and 9±5 years among children. More parents that completed questionnaires were female (65%) compared to male (46%). Serious comorbidities were uncommon but included 109 (24%) patients with asthma, hypertension 79 (18%), and diabetes 22 (5%).

Access to Care

One-third of study participants denied having a primary care doctor (Table 1). The majority of patients (55%) also denied phone access to a nurse or clinician for advice. Female participants reported higher access to primary care than men. Adults were less likely to have telephone access for healthcare advice compared to parents of children (OR 0.49, 95% CI, 0.32 – 0.74). Males were less likely than females to have access to healthcare advice (OR 0.52, 95% CI, 0.37 – 0.74). Only 342 (61%) of patients reported computer internet access, but 538 participants reported access to mobile internet use (96%). There was no difference in mobile internet capacity between gender and age. Participants reported seeking medical advice from

Table 1. Access to healthcare and internet services.

		All, n (%)	Male, n (%)	Female, n (%)	p-value
Provider Access	Primary care provider	372 (66)	111 (56)	261 (73)	<0.001
	Clinic/nurse phone line*	253 (45)	70 (35)	183 (50)	<0.001
Online Acess	Phone applications	414 (76)	151 (77)	263 (75)	0.693
	Computer internet access	342 (61)	120 (60)	222 (62)	0.698
	Phone internet access	538 (96)	190 (95)	348 (97)	0.331
Primary Health Resources	Friends or family	375 (67)	127 (64)	248 (69)	0.194
	Medical reference book	205 (37)	67 (34)	138 (38)	0.255
	Online medical search	382 (68)	126 (63)	256 (71)	0.048

*Access to nurse or clinician after-hours phone line to call for medical advice.

Table 2. Response to mobile health tool.

	Response, n (%)			
Willingness to use mHealth tool to triage current condition	Definitely 314 (56)	Probably 198 (36)	Unsure 28 (5)	Unlikely 19 (3)
Response if mHealth tool suggests that current condition is low risk	Visit Clinic 165 (30)	Use Telemedicine 62 (11)	Watchful Waiting* 152 (28)	Seek ED Care 170 (31)

mHealth, mobile health; *ED,* emergency department.
*Watchful waiting indicates that the patient was willing to manage symptoms at home with over-the-counter medications and later determine if medical attention was needed.

internet resources as often as friends or family members. The most commonly used internet resources were Google (66%) and WebMD (14%).

Willingness to Use Mobile Health

Most participants (92%) indicated that they would use a mHealth application to assist in triaging their current condition (Table 2). Among those who indicated they would be unlikely to use a mHealth application, the most common reasons were having ready access to a physician; no access to a reliable phone; or a preference for an individual assessment. The majority of patients indicated that they would avoid an ED visit if the mHealth tool suggested that their current health issue was low risk for a health emergency (Table 2).

DISCUSSION

Our results show that access to primary care providers for both clinic visits and medical triage advice is poor in this underserved population. Our study found that women had increased medical access, which is consistent with the current literature.[5] Nevertheless, this community has high rates of mobile phone use, internet capability, and patients who use the internet to research their symptoms. These results contrast to a 2012 study that found that only 21% of an underserved population used the internet for health information compared to 61% of the general population.[6] A 2015 study found 71% of ED patients had smartphones and 44% of smartphone users had health applications.[7] Our study consisted of a much larger cohort of ED patients and found that nearly every participant had access to internet cell phone use. This difference likely reflects a younger cohort and increasing access to mobile phones.

Our results show that ED patients with low-acuity complaints are willing to use a validated application to assist in triage for their condition. The vast majority of patients said they would "definitely" or "probably" use a validated application. Additionally, nearly 70% of participants were willing to choose non-emergent healthcare for their current condition if they had access to a reliable mHealth tool that indicated low risk of medical emergency.

A validated mHealth tool has the potential to assist in making important decisions as to where and when to seek care. Particularly in underserved populations, such a tool has the potential to decrease ED visits and lower healthcare costs.[8] Despite this potential, the willingness of underserved populations to use mHealth requires further study. Participants who responded to our hypothetical scenario were already under the care of a healthcare provider and may have been reassured answering in the manner they did than if they were to

consider such questions prior to coming to the ED. We did not apply a triage mHealth tool in practice prior to arrival. Furthermore, some existing data suggests that patients make inconsistent decisions based on mHealth data.[7] Low health literacy may also be a factor that prevents patients from adequately interacting with mHealth tools to make informed decisions.[9]

Whether mHealth tools are ready to address these disparities remains to be seen. Symptom checkers have proliferated through web-based or app-based mHealth resources. These tools typically use algorithms (often enabled by artificial intelligence) to help patients with self-diagnosis or self-triage. Nevertheless, validation of these tools is lacking. In one study testing whether 23 different symptom checkers could provide accurate triage, correct triage of non-emergent cases was relatively poor (55%).[10] The authors note that symptom checkers are generally risk adverse and err toward recommending emergent care more often than is necessary. Nurse-staffed telephone triage lines may also err toward recommending emergent care more often than is necessary. There is evidence that physician-based telemedicine triage tools are equivalent to in-person physician triage tools.[11] However, whether improved mHealth algorithms can outperform nurse-staffed triage remains to be seen.

LIMITATIONS

There are several notable limitations. First, results from this convenience sample of eligible, low-acuity patients may not translate to a broader group of ED patients, non-English speakers, and other underserved populations. We targeted a population of young patients and parents in this study. Older ED patients likely experience access to care and use of mHealth differently. Second, we designed and refined our survey instrument based on limited existing literature and patient response. The instrument did not undergo rigorous validation prior to data collection. Finally, it is notable that primary care access remains a barrier. Even though patients may be willing to use mHealth tools for triage purposes, these tools may reduce low-acuity ED visits if primary care or urgent care access is poor.

CONCLUSION

In an urban, low-income community of young adults and parents of children, there is a high degree of capacity and willingness to implement mHealth technology to guide medical triage. In settings where adequate healthcare access may be lacking, these results highlight the potential for mHealth to reduce disparities related to medical triage.

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Conflicts of Interest: By the WestJEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. This study was supported by an internal departmental grant through Henry Ford Hospital.

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Techniques to Shorten a Screening Tool for Emergency Department Patients

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Section Editor: Jacob Manteuffel, MD
Submission history: Submitted March 2, 2019; Revision received July 9, 2019; Accepted July 9, 2019
Electronically published: August 20, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.42938

Introduction: Screening of patients for opioid risk has been recommended prior to opioid prescribing. Opioids are prescribed frequently in the emergency department (ED) setting, but screening tools are often of significant length and therefore limited in their utility. We describe and evaluate three approaches to shortening a screening tool: creation of a short form; curtailment; and stochastic curtailment.

Methods: To demonstrate the various shortening techniques, this retrospective study used data from two studies of ED patients for whom the provider was considering providing an opioid prescription and who completed the Screener and Opioid Assessment for Patients with Pain-Revised, a 24-item assessment. High-risk criteria from patients' prescription drug monitoring program data were used as an endpoint. Using real-data simulation, we determined the sensitivity, specificity, and test length of each shortening technique.

Results: We included data from 188 ED patients. The original screener had a test length of 24 questions, a sensitivity of 44% and a specificity of 76%. The 12-question short form had a sensitivity of 41% and specificity of 75%. Curtailment and stochastic curtailment reduced the question length (mean test length ranging from 8.1-19.7 questions) with no reduction in sensitivity or specificity.

Conclusion: In an ED population completing computer-based screening, the techniques of curtailment and stochastic curtailment markedly reduced the screening tool's length but had no effect on test characteristics. These techniques can be applied to improve efficiency of screening patients in the busy ED environment without sacrificing sensitivity or specificity. [West J Emerg Med. 2019;20(5)804-809.]

INTRODUCTION

Screening tools have been developed for emergency department (ED) patients to help detect multiple diseases and risk factors, ranging from nutrition status to sepsis to suicide risk.[1-3] These tools vary in length and the time needed to complete them, and utilization is likely impacted by competing interests, priorities and ease of use. In the busy ED environment, brevity – while maintaining accuracy – is of the essence.

The United States is in the midst of an opioid crisis: an average of 134 people per day died due to an opioid-related overdose in 2017.[4] The crisis was declared a national public health emergency in 2017.[5] The ED is at the epicenter of the opioid crisis, for its role in prescribing opioids for acute pain, treating medical complications of injection drug use, and treating opioid use disorder. It is an area where screening for opioid risk could potentially be impactful.[6] Although emergency physicians provide a relatively small amount of opioids compared with other specialties,[7,8] there is evidence that the first opioid prescription

given in the ED can portend long-term opioid use.[9,10] Therefore, screening for opioid-related risk prior to a new prescription from the ED would be prudent and is also in alignment with multiple guidelines, including those by the Centers for Disease Control and Prevention and multiple cities and states.[11-13]

Unfortunately, the exact definition of what it means to "screen" a patient is unclear. Available screening tools vary in length but typically require many questions. For example, the full-length Drug Abuse Screening Test has 20 questions. The Opioid Risk Tool is 10 questions in length, but each answer is associated with a different point value and is also different for females vs males.[14] The Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), perhaps the most rigorously studied and validated screening tool for opioid-related risk in the ED setting and elsewhere, is 24 questions in length,[15-16] quite long for a tool that could be administered to every ED patient receiving an opioid prescription. Previous work has evaluated administering the SOAPP-R on a tablet computer as a means to allow patients to complete the screener and have their results tallied without additional ED staff time required.[17] But for this and other screening tools used in the ED environment, discovering a way to shorten the actual number of questions required may make the screening tools more desirable for implementation.

The purpose of this study was to describe and explore three ways to reduce the length of a screening tool. Using SOAPP-R as an example, we studied shortened forms as well as techniques called curtailment and stochastic curtailment, which we define in detail below. The ultimate goal was to shorten the screening tool while not losing predictive value. Our secondary aim was to inform the reader about these techniques, which may be applied to other screening tools as well.

Population Health Research Capsule

What do we already know about this issue?
Several opioid screening tools have been implemented in the ED setting, but their acceptance has been limited, likely due to their length.

What was the research question?
Can shortening techniques such as curtailment and stochastic curtailment be applied to an opioid screening tool?

What was the major finding of the study?
An opioid screening tool can be shortened considerably without losing predictive power.

How does this improve population health?
Techniques such as short forms, curtailment, and stochastic curtailment can be used to shorten screening tools, which may increase their use in the ED setting.

METHODS

The study is a retrospective evaluation of SOAPP-R results from two prospectively enrolled convenience samples of ED patients for whom the emergency provider was considering prescribing an opioid to treat pain. The first cohort included 82 adult patients presenting to an urban, academic trauma center in Massachusetts with approximately 42,000 annual visits between May–August 2013. The second cohort included 106 adult patients presenting to an urban, academic trauma center in Colorado with approximately 100,000 annual visits between June–August 2016. The study was approved by the institutional review boards at both institutions. We did not calculate an a priori sample size as this was an analysis of preexisting data and the purpose of this paper was to demonstrate various shortening techniques.

The methodology and results have been described elsewhere in depth.[17,18] Briefly, to be eligible for enrollment, patients had to have had an acute, painful condition for which the treating emergency physician was considering treating with an opioid analgesic. Patients completed SOAPP-R on a tablet computer; they were informed that the results would not be shared with their treating physician. The tablet computer recorded patients' answers on the screening tool. The physician also accessed each patient's prescription drug monitoring program (PDMP) record, and a trained research assistant recorded the number of Drug Enforcement Administration schedule II–V medications, subset number of opioids, number of prescribers used for all schedule II–V medications, and number of pharmacies used to fill these medications in the previous 12 months. For the purpose of the study, we defined a high-risk prescription history as having ≥4 opioid prescriptions and ≥4 providers for schedule II–V medications in the previous 12 months, as has been used in prior research.[19,20]

For this study, we applied three techniques to shorten the full-length screening tool: short form; curtailment; and stochastic curtailment (SC). Creation of the 12-question short form has been described previously.[21] In sum, LASSO (least absolute shrinkage and selection operator) logistic regression was used to determine which questions to include. The 12-question version had screening characteristics similar to the full-length version and the highest acceptance by an expert panel.[21] Although initially a cutoff score of 10 or greater was suggested, further work determined that a score of 9 or greater indicating high risk produced the best test characteristics.[22] This short form can be administered on paper, similar to the original SOAPP-R.

As opposed to the fixed-length short form, curtailment is a variable-length testing method. With curtailment, a computer (such as a tablet or smartphone) analyzes each response as it is

entered and determines a) whether the number of points on the screening tool meets criteria for the respondent to be at risk, or b) whether the respondent could not achieve a number of points sufficient to be at risk with the number of questions remaining. As an example, the SOAPP-R contains 24 questions with a possibility of 0-4 points for each question. Having a score of 18 or higher indicates "high risk." Once a respondent has 18 points, the screener ends as they are already determined to be high risk. Conversely, if the respondent has a cumulative score of no greater than 13 after the first 23 items, it would be impossible to be high risk even if they received four points for the final question; so it would end after the 23rd question. With this methodology, the number of questions varies for each individual, depending on how they respond to questions.

Stochastic curtailment is another stopping rule that halts testing not only at the same time that curtailment does, but in other specific circumstances as well. Specifically, SC also stops early when there is either a high probability that the full-length questionnaire will provide a high-risk classification (in which case stochastic curtailment makes an immediate classification of high risk), or a high probability that the full-length questionnaire will provide a low-risk classification (in which case SC makes an immediate classification of low risk). A typical cut-off would be a 95% probability, so that if a subject has a 95% or greater chance of being high risk based on previous answers, the screening tool would end. Again, the number of questions would vary for each participant but the length would be shorter than simple curtailment in most scenarios. Previous research on other screening tools (CES-D, COMM and Medicare Health Outcomes Survey) determined that the number of questions can be decreased by over 50% while having the same predictive outcome as the original screening tools at least 97% of the time.[23-25] For this study, we evaluated probabilities of 95% (SC-95) and 99% (SC-99). Data analysis was performed with R (www.r-project.org).

RESULTS

From the original studies, the following test characteristics were determined. In the first cohort, 93 patients were approached and 82 patients (88.2%) completed the study and had complete data. The mean score on SOAPP-R was 16.0 (standard deviation [SD] 12.8). Twenty-seven patients (32.9%) had a score ≥18. The test characteristics of SOAPP-R to detect high-risk prescription history were sensitivity 54% and specificity 71%. In the second cohort, 154 patients were approached and 106 patients (68.8%) completed the study and had complete data. The mean score on SOAPP-R was 12.8 (SD 10.3). Twenty-five patients (23.6%) had a score ≥18. The test characteristics of SOAPP-R to detect high-risk prescription history in this cohort were sensitivity 38% and specificity 80%. Combining the two cohorts (n=188), the sensitivity was 44% and the specificity was 76%.

The test characteristics for the full-length SOAPP-R, a shortened 12-question SOAPP-R with cutoff score of ≥9, curtailment, and stochastic curtailment (SC-95 and SC-99) are demonstrated in Table 1. The short form reduced the number of questions from 24 to 12 at the expense of a slightly decreased sensitivity (44% to 41% in the combined cohort). Curtailment and both techniques of stochastic curtailment produced nearly identical test characteristics as the original SOAPP-R, but with markedly decreased numbers of questions (from 24 questions to a mean of 19.7 for curtailment, 11.8 for SC-99 and 8.1 for SC-95) in the combined cohort.

DISCUSSION

In our study, we have demonstrated that it is possible to shorten an opioid-risk screening tool for ED patients. Versions using curtailment and stochastic curtailment would have shortened the number of questions for the vast majority of patients. Furthermore, the diagnostic accuracy of these tests was about the same as the original screener in every permutation. Indeed, in the combined cohort, the 95% probability SC had a mean test length of 8.1 (compared to 24 questions for the full screener), and essentially unchanged sensitivity and specificity. Only the fixed-length, 12-question short form had a slightly decreased sensitivity, which is likely to be irrelevant in clinical practice.

The sensitivity and specificity when using curtailment are just as high as those of the full-length screener because the technique tracks the respondent's answers and only stops early when the classification of the full-length screener has been determined with certainty, making the exact same classification that the full-length screener would make. Similarly, stochastic curtailment only stops early when the classification of the full-length screener has been determined to a high level of probability. For all of these versions, the sensitivity was low and the specificity was higher. Therefore, in this clinical situation each version of the SOAPP-R exhibited greater success in identifying low-risk patients than in identifying high-risk patients.

The practical limitation with curtailment and stochastic curtailment is that they require the use of a computer to administer. Our previous work demonstrated that ED patients can use a tablet computer to perform screening and that they have little difficulty and high satisfaction using the tablet for this purpose.[17] Still, there are several downsides to be considered, such as the need to safely store, charge and clean the tablet between patient use, as well as the possibility of theft and the added expense of purchasing a device.

There are other options with potential applicability to the ED setting. It is possible to reduce the reduce the length of the SOAPP-R to a uniform 12 questions, as previously described, or even down to eight questions.[21, 26] Regarding these short forms, which do not require a computer to administer, their sensitivity and specificity would be expected to be similar to those of the full-length screener because the short forms were developed specifically to retain the items most predictive of the outcome. In developing the 12-item test, questions from the original SOAPP-R asking about aberrant use of pain medication, such as how often the medication ran out early or how often the

Table 1. Test characteristics of the full-length and shortened screening tools.

Cohort 1 (n=82)					
	Sensitivity	Specificity	Mean Number of Questions	SD of Test Length	% of Tests Shortened
Full-length SOAPP-R	0.54	0.71	24.0	0.0	0.0
Shortened SOAPP-R	0.46	0.71	12.0	0.0	100.0
Curtailment	0.54	0.71	19.1	5.3	85.4
SC-99	0.54	0.71	12.3	6.4	87.8
SC-95	0.54	0.74	8.2	6.2	95.1

SD, standard deviation; *SOAPP-R,* Screener and Opioid Assessment for Patients with Pain-Revised; *SC,* stochastic curtailment.

Cohort 2 (n=106)					
	Sensitivity	Specificity	Mean Number of Questions	SD of Test Length	% of Tests Shortened
Full-length SOAPP-R	0.38	0.80	24.0	0.0	0.0
Shortened SOAPP-R	0.38	0.79	12.0	0.0	100.0
Curtailment	0.38	0.80	20.2	4.4	88.7
SC-99	0.38	0.80	11.4	6.0	95.3
SC-95	0.38	0.80	8.0	6.1	100.0

SD, standard deviation; *SOAPP-R,* Screener and Opioid Assessment for Patients with Pain-Revised; *SC,* stochastic curtailment.

Cohort Combined (n=188)					
	Sensitivity	Specificity	Mean Number of Questions	SD of Test Length	% of Tests Shortened
Full-length SOAPP-R	0.44	0.76	24.0	0.0	0.0
Shortened SOAPP-R	0.41	0.75	12.0	0.0	100.0
Curtailment	0.44	0.76	19.7	4.8	87.2
SC-99	0.44	0.76	11.8	6.2	92.0
SC-95	0.44	0.77	8.1	6.1	97.9

SD, standard deviation; *SOAPP-R,* Screener and Opioid Assessment for Patients with Pain-Revised; *SC,* stochastic curtailment.

individual used more pain medication than they were supposed to, were the most predictive of the outcome. Conversely, the questions asking patients if they felt bored or had any close friends with an alcohol or drug problem were the least predictive. Notably, the technique of curtailment does not itself provide an indication of which items are most (and least) predictive of the outcome, nor does it allow us to determine the number of items to be administered in advance. Taking the process a step further, it is then possible to administer the shorter static forms on a computer and apply curtailment techniques, reducing the number of questions even more.[27] All of this work supports the concept that lengthy screening tools that have been developed for non-ED settings can potentially be repurposed and made more efficient for the frenetic and time-sensitive environment of the ED without a negative effect on the predictive value of the screening tool.

It should be noted that this study serves to demonstrate the concept of shortening the SOAPP-R but does not yet provide compelling evidence that this particular screening tool should be used in the ED setting. A recent systematic review comparing SOAPP-R and other commonly used opioid-screening tools found that the validity and reliability of all of the screeners they investigated were lacking and could not be validated for use in the ED setting.[28] Our studies of the SOAPP-R, for example, are based on patients with four or more providers for four or more opioid prescriptions in the prior 12 months. That cutoff was chosen empirically as a higher risk quality, but has not yet been adequately tied to a concrete clinical outcome such as overdose death. Furthermore, another study discovered that about two-thirds of patients who presented to an ED with opioid dependence had no prescriptions documented in their state PDMP, indicating

that it is an imperfect outcome measure.[29]

Recently, there has been work to shorten other screening tools for ED use. For example, a study evaluating the Beck Scale for Suicide Ideation was amenable to computer adaptive testing, in which the next question administered was dependent on the patient's answer to the previous questions.[30] Similar findings had been previously described in non-ED patients as well.[31] With this methodology, the 19-question score could be reduced to just four questions in both studies. Future work like this, in which questions are asked in a non-linear fashion and the screener is ended when there is significant probability of detecting a result shows great promise for future computer-based screening.

LIMITATIONS

The study is subject to the same limitations as the source studies, including that patients were enrolled in a convenience sample fashion, non-English speaking patients were excluded, and that the "gold standard" outcome measure of four or more opioid prescriptions and four or more prescribers for controlled substances in 12 months was imperfect. However, the primary goal of the paper was to demonstrate the applicability of various shortening techniques on a tool that could be used in the ED environment. This was a real-data simulation study that may produce different results than a prospectively collected sample. As an example, test results were determined post hoc based on subjects' responses on the full length SOAPP-R. With the short form, certain questions are eliminated and context effects – how a preceding question affects how a respondent answers a subsequent question – may cause variation not detectable by our methods.

CONCLUSIONS

In an ED population completing computer-based screening, the techniques of short forms, curtailment and stochastic curtailment markedly reduced the screening tool's length but had negligible effects on test characteristics. These techniques can be applied to improve the efficiency of screening tools used in the busy ED environment.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Evaluation of a Standardized Cardiac Athletic Screening for National Collegiate Athletic Association (NCAA) Athletes

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Section Editor: Laleh Gharahbaghian, MD
Submission history: Submitted March 24, 2019; Revision received May 9, 2019; Accepted July 10, 2019
Electronically published August 14, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.43190

Introduction: Sudden cardiac death is a rare cause of death in young athletes. Current screening techniques include history and physical exam (H and P), with or without an electrocardiogram (ECG). Adding point of care cardiac ultrasound has demonstrated benefits, but there is limited data about implementing this technology. We evaluated the feasibility of adding ultrasound to preparticipation screening for collegiate athletes.

Methods: We prospectively enrolled 42 collegiate athletes randomly selected from several sports. All athletes were screened using a 14-point H and P based on 2014 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, ECG, and cardiac ultrasound.

Results: We screened 11 female and 31 male athletes. On ultrasound, male athletes demonstrated significantly larger interventricular septal wall thickness ($p = 0.002$), posterior wall thickness ($p < 0.001$) and aortic root breadth ($p = 0.002$) compared to females. Based on H and P and ECGs alone and a combination of H and P with ECG, no athletes demonstrated a positive screening for cardiac abnormalities. However, with combined H and P, ECG, and cardiac ultrasound, one athlete demonstrated positive findings.

Conclusions: We believe that adding point of care ultrasound to the preparticipation exam of college athletes is feasible. This workflow may provide a model for athletic departments' screening. [West J Emerg Med. 2019;20(5)810-817.]

INTRODUCTION

Sudden cardiac death is a rare but leading cause of death in young athletes on the playing field.[1] These deaths are usually due to unsuspected heart disease, as many conditions are not detected by routine screening measures.[2] National Collegiate Athletic Association (NCAA) athletes partake in rigorous training programs at an elite level. For collegiate athletes with a previously undiagnosed cardiac condition, the activity during training and competition places them at high risk for sudden cardiac death. The causes of sudden death in athletes under the age of 35 include hypertrophic cardiomyopathy (HCM), coronary artery anomalies, long QT syndrome, and infections such as myocarditis.

There are approximately 75 terminal outcomes per year

in the United States in athletes between the ages of 13 and 25 years (89% occurring in males) with the majority immediately after exercise.[3-5] New findings from an Italian Registry show a reduction of sudden death in athletes over the past decade due to enhanced screening of athletes, aged 16 and older.[6] Pre-participation cardiovascular screening in athletes can uncover some of the underlying conditions contributing to this risk.[7,8] The American Heart Association (AHA) and American College of Cardiology (ACC) Guidelines support screening with a 14-point history and physical examination (Appendix 1).[9] However, studies have shown that the current screening techniques are insensitive in diagnosing many cardiac conditions.[7,8] Early screening of patients at risk may improve the identification and early prevention of these cardiovascular events.[10] Despite this data, there is still no universal and standardized applied screening method for incoming student athletes.[11]

A history and physical (H and P) examination without an electrocardiogram (ECG) are of questionable value and have not demonstrated cost-effectiveness due to their poor sensitivity and specificity.[12,13] Prior studies have determined that routine screening with ECG and physical exam alone can detect some abnormalities.[14-18] However, an issue posed by the AHA is the implication of medical liability in the current climate where no standardized means exist to clear student athletes for sport if they are deemed inappropriate to participate based on ECG findings.[11] Other studies indicate that by providing a more standardized means for ECG analysis will provide a more homogenous and consistent interpretation of ECG screenings.[19-20] In this study we aimed to assess the feasibility of conducting point of care cardiac ultrasounds in addition to routine preparticipation screening in collegiate athletes.

Population Health Research Capsule

What do we already know about this issue?
Sudden cardiac death is a rare cause of death in young athletes, usually due to unsuspected heart disease. However, there is still no standardized screening method.

What was the research question?
We assessed cardiac ultrasound in addition to routine preparticipation screening in collegiate athletes.

What was the major finding of the study?
Point-of-care ultrasound can be used to screen athletes for hypertrophic cardiomyopathy (HCM).

How does this improve population health?
Future large-scale studies are needed to validate our promising findings and determine if ultrasound can be used as a screening tool for HCM.

METHODS

This study was approved by the site Clinical Review Board and the Institutional Review Board. Written, informed consent was obtained from all patients enrolled before any history, screening or ECG was completed. Our institution performs a standard 14-point ACC/AHA Pre-participation History and Physical Exam (PPE) and ECG on all incoming athletes during their freshman year. For this study, we offered a limited cardiac ultrasound exam as one additional component to the annual screenings.

Subject Recruitment and Selection of Subjects

All male and female NCAA Division 1 student-athletes older than 18 years of age at our institution were invited to voluntarily participate during their intake collegiate athlete physical examination and cardiovascular screening visit. Potential subjects were recruited by convenience sampling. Athletes with previously known cardiac abnormalities were included in the study. Exclusion criteria included any athlete less than 18 years of age, all walk-on athletes (athletes not recruited or offered scholarship), or those not deemed part of the athletic program prior to the commencement of the academic year. Student athletes who did not agree to the study consent were excluded. Written consent was obtained from all athletes prior to participation.

Athlete Screening Workflow

All student-athletes completed their health history forms. A physical exam was then completed by one of the board-certified Sports Medicine physicians at the first station. At the second station, a trained ECG technician performed the ECG. During the process, a cardiology fellow was present and performed a preliminary read on the ECG. They were then read by an attending cardiologist using compiled ECG parameters from both the 2010 European Society of Cardiology Criteria and the Seattle Criteria (Refined Criteria) specific for athletes.[19,21] Upon collection of the health history and physical exam information and ECG, the research team then performed a point of care cardiac ultrasound. All point of care ultrasounds were performed by trained emergency medicine resident physicians. These physicians received a 30-minute hands-on training session from the site ultrasound director. The data from these cardiac ultrasounds were then evaluated in real time by attending cardiologists with training in echocardiography. If abnormal findings on the ECG, physical examination or cardiac ultrasound were noted, these were immediately reviewed by one of the supervising cardiologists. If ECG or ultrasound abnormalities were

confirmed, a full cardiac ultrasound and magnetic resonance imaging (MRI) were scheduled as a same week appointment with the Sports Cardiology clinic for further evaluation.

In summary, the overall workflow of athlete screening proceeded as follows:

1. Student athletes scheduled by the Athletic Department for their PPE, ECG, and point of care cardiac ultrasound exam.

2. Check in, voluntary Screening Registry introduction and informed consent provided to interested athletes.

3. Clinical visit with the physician to review 14 point AHA/ACC history and complete cardiac physical exam.

4. ECG is performed and reviewed (preliminary) by Sports Medicine or Cardiology Fellow.

5. Point of care cardiac ultrasound is performed and reviewed (preliminary) by Sports Medicine or Cardiology Fellow.

6. Abnormal ECG or cardiac ultrasound images are immediately shared and reviewed with attending Cardiologist.

7. All ECGs are reviewed by attending Cardiologist, then scanned into the athletes' chart associated with their Cardiac Screen visit note.

8. For confirmed abnormal ECG or cardiac ultrasound, physical exam finding (heart murmur), or any other indication, a point of care cardiac ultrasound is arranged and a follow-up appointment (same week) is made with the Sports Cardiology clinic.

9. If no abnormalities are found (or confirmed), the student athlete may be cleared for the participation.

10. For student athletes who enter the athletic program at different times of year or have concerning cardiovascular events, the Sports Medicine faculty and Athletic Trainer perform an interim PPE and point of care ECG. These findings are immediately reviewed with the cardiology fellows and faculty on call. Abnormal ECG, cardiac ultrasound, physical exam finding, or event will lead to next day formal cardiac ultrasound and same week Sports Cardiology clinic visit. For more life-threatening events, athletes are transported to the nearest Emergency Department and Sports Cardiology fellow and faculty will be available by pager for stat consultation.

Point of Care Cardiac Ultrasound Measurements

Based on American Society of Echocardiography guidelines, the inner left ventricular diameter breadth, interventricular septal wall thickness, posterior wall thickness, and the aortic root breadth were measured during diastole. All measurements were obtained using the parasternal long axis view with the patient lying in a supine position.[22]

Data Analysis

This registry did not duplicate the routine athletic screening process at our institution. All student athletes completed questionnaires during their screening session. Demographic data included gender, age, race and ethnicity, number of sports in which they compete, and specific sport was collected. Relevant family and personal cardiac health history were collected using the 14-point AHA/ACC history. Physical exam data was tabulated following the complete cardiac physical exam. The history and physical exams were recorded on paper and kept in the athlete's permanent medical record prior to data entry in the registry. ECG and point of care cardiac ultrasound data were collected following interpretation by an attending cardiologist. All relevant data points were entered into a REDCap database. Male and female athletes were compared for differences in ECG and ultrasound measurements using unpaired Student's t-test for continuous variables and Two-Proportion z-Test for categorical variables. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using R statistical programming software version 3.4.2, (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

50 athletes were approached for enrollment in the study. 42 athletes were screened with history and physicals from the available population in two days. The point of care ultrasound added approximately 7 minutes to each athlete's screening. Most of this time was required for uploading and analyzing ultrasound images rather than image acquisition. The study group consisted of 11 female and 31 male athletes, with mean average ages of 18.5 and 18.6 years, respectively. Table 1 demonstrates demographics of all screened athletes. As shown in Figure 1, we screened 21 football, 10 male basketball, 2 female basketball, 5 softball, 2 female volleyball, 1 female rowing, and 1 female field hockey athletes.

H and P data demonstrated relatively benign family cardiac histories with collective family heart disease history prevalence less than 30% (Table 2). Personal cardiac histories most notably demonstrated a 12.9% prevalence of heart murmurs in males, and a 27.3% prevalence of syncope history in females. 19.4% of males and 9.1% of females reported a history of formal cardiac screening.

Overall, 41 of 42 athletes subsequently completed full ECG and ultrasound testing. We account for 41 of the 42 athletes on account that one of the athletes left before the ultrasound exam could be complete. Comparing male and female athletes, the two groups differed significantly in multiple ECG measurements. On average, males demonstrated longer QRS duration (98.2 milliseconds (ms) vs 90.0 ms, $p = 0.004$), and a higher proportion of athletes with J-point elevation (53.3% vs 18.2%, $p = 0.044$). Ultrasounds also demonstrated multiple significant differences. Males had significantly larger interventricular septal wall thickness (1.0

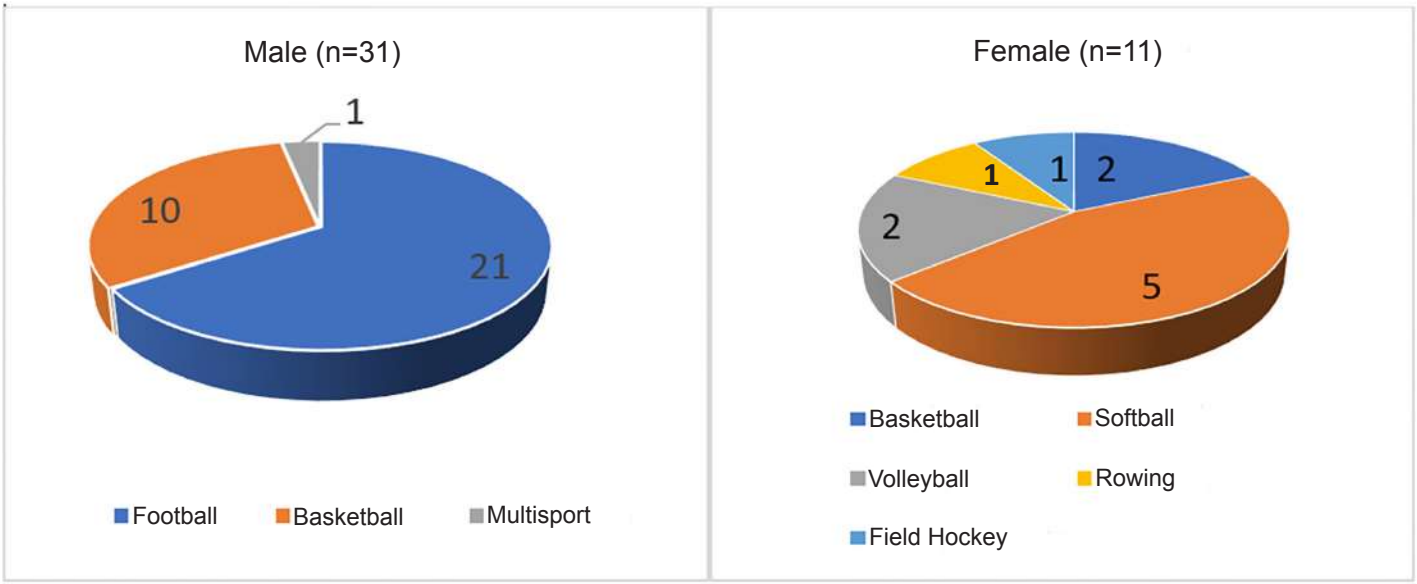

Figure 1. Screened athletes by sport.

centimeter [cm] vs 0.8 cm, p = 0.002), posterior wall thickness (1.1 cm vs 0.8 cm, p <0.001) and aortic root breadth (2.7 cm vs 2.3 cm, p = 0.002) (Table 3).

Based on H and P and ECGs separately, and when combining H and P with ECG, none of the 42 athletes demonstrated a positive screening for cardiac abnormalities. However, based on combined H and P, ECG, and point of care cardiac ultrasound data, one athlete demonstrated positive findings. This athlete was African American and demonstrated questionable findings in his H and P and ECG (Figure 2): he had a history of a heart murmur and notable ST elevations in his lateral leads (V1-5) with deep T wave inversions in II, III and V4, he also had a first-degree atrioventricular block.

These findings were consistent with refined Seattle criteria and would have warranted additional follow up. Coupled with his abnormal cardiac ultrasound findings, there was significant cause for concern, as he had an apparent enlarged left ventricle with a posterior wall diameter of about 1.3cm (Figure 3). Due to these concerning findings, he warranted additional imaging and follow up as an outpatient with cardiology and a cardiac MRI. The athlete's follow-up cardiac MRI was evaluated as normal, although the athlete was found to have concentric left ventricular hypertrophy with a septal thickness of 1.3 cm most consistent with an athletic heart (Figure 4). Ultimately, the athlete was cleared for full participation.

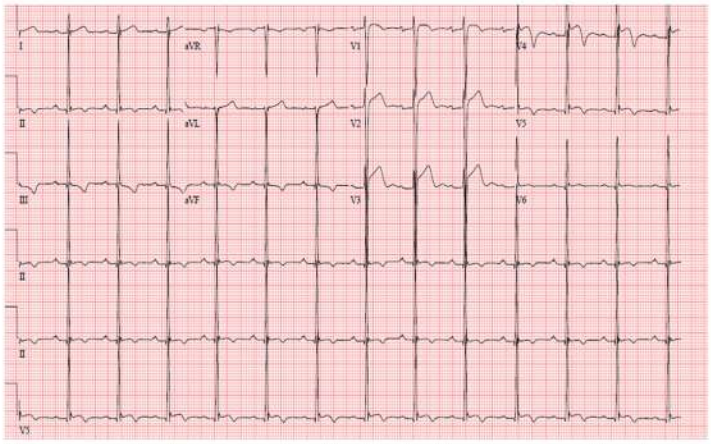

Figure 2. Electrocardiogram of athlete requiring follow up.

DISCUSSION

Many studies indicate that the history and physicals alone are poor representations of the actual assessed risk for pre-participation because of the low sensitivity and specificity of these findings.[12] The ECG has been proposed as an inexpensive screening tool which may be added to the history and physical exam to identify athletes at risk.[10] In fact, as mentioned by Harmon et al., the ECG can have important implications for primary prevention of sudden cardiac death. Estimates of the effectiveness of ECGs through screening alone range from 66% to 100%.[8,23] Due to the low sensitivity of standard histories and variability of practices with ECG, many have proposed the addition of point of care cardiac ultrasound to routine screening procedures.

Although minimal significant cardiac abnormalities were identified in this study with the addition of point of care cardiac ultrasound, we were able to demonstrate efficiency in conducting pre-participation screening for athletes involving a comprehensive exam with point of care cardiac ultrasound. In our athlete population, we were able to obtain all four target ultrasound measurements in 100% of our athletes. As ultrasound becomes integrated into routine care models, it is reasonable to anticipate that non-cardiology trained physicians would be able to perform and interpret these exams.[24,25]

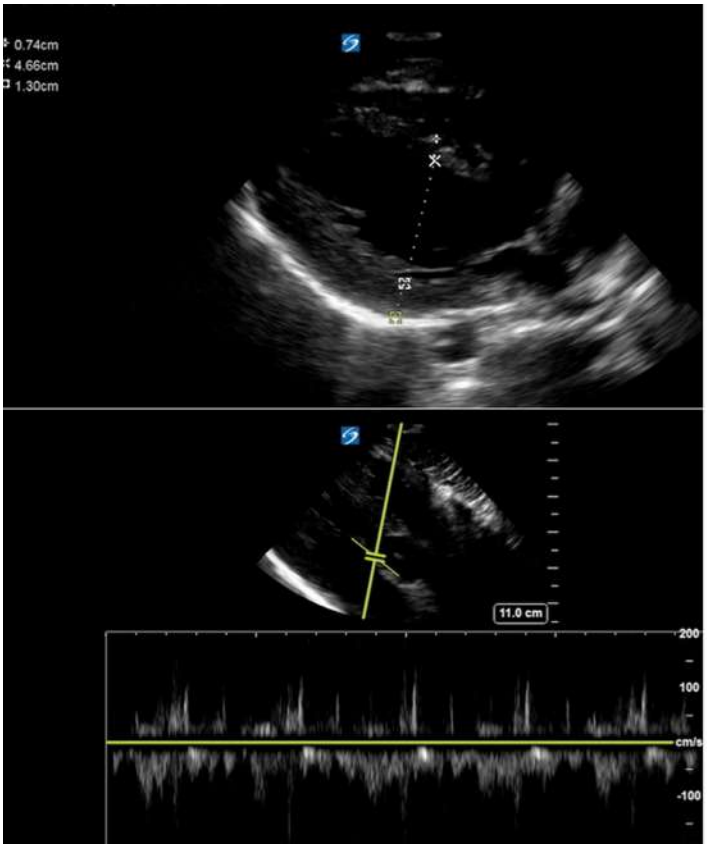

Figure 3. Ultrasound images of positive findings of point of care cardiac study. Posterior wall thickness of 1.3 centimeters coupled with the abnormal history and physical findings were concerning for this athlete.

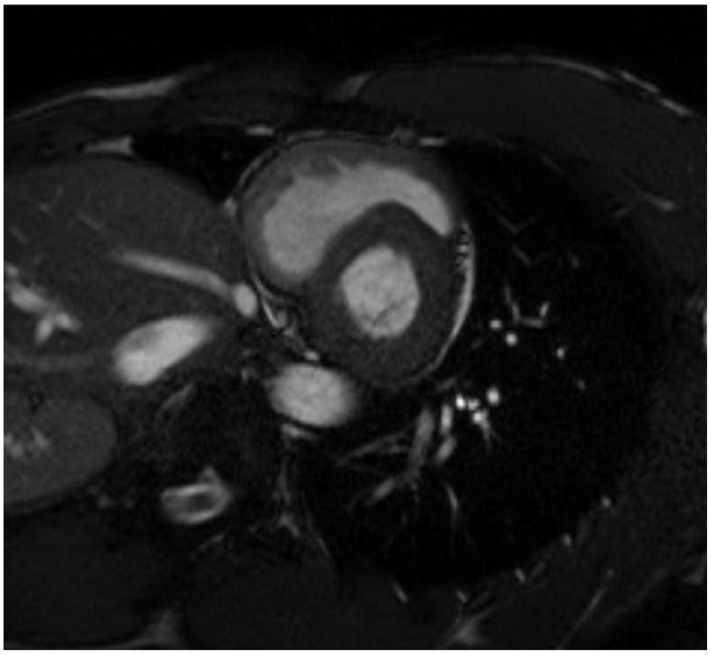

Figure 4. Still image from the cardiac magnetic resonance image of the positive athlete: Demonstrating concentric left ventricular hypertrophy with a septal thickness of 1.3 centimeters most consistent with an athletic heart.

Table 1. Demographics of screened athletes.

Demographic	Male (n=31)	Female (n=11)
Age*, y	18.6 (18-22)	18.5 (17-22)
Hispanic/Latino, n	0	1
African American, n	21	2
Caucasian, n	10	9

*Mean (range)

Table 2. History and physical exam profiles of screened athletes.

	Male (n=31)	Female (n=11)
Physical exam findings		
Height* (centimeters)	190.8 (177.8-207.8)	175.8 (166.4-191.8)
Weight* (kilograms)	99.2 (73.8-153.4)	74.6 (62.1-88.5)
History findings**		
Family Hx heart disease	29.0	18.2
Family Hx hypertension	54.8	18.2
Family Hx unexplained syncope	3.2	0.0
Family Hx stroke	0.0	9.1
Family Hx pacemaker	0.0	9.1
Family Hx death < 50 years old	0.0	0.0
Family Hx structural heart disorder	0.0	0.0
Family Hx arrhythmia	0.0	0.0
Family Hx Marfan Syndrome	0.0	0.0
Personal Hx hypertension	0.0	0.0
Personal Hx heart murmur	12.9	9.1
Personal Hx formal cardiac screening	19.4	9.1
Personal Hx syncope during exercise	6.4	27.3
Personal Hx chest pain after exercise	3.2	9.1
Personal Hx pacemaker	0.0	0.0

Hx, history.
*Mean (range).
**History findings reported as % male or females screened.

Based on our institution's experience in coordinating this effort, this study is replicable if four key conditions are met: (1) an athlete's individual screening occurs on a single-day; (2) the cardiac ultrasound creates minimal time disruptions to routine procedures; (3) ultrasound equipment is freely available for study team use; and (4) the presence of an attending cardiologist at the screenings is standard of care. First, due to our single-day screening format, all personnel, ultrasound equipment, and ECG equipment required for the study are preemptively coordinated to participate with minimal effort.

Table 3. Electrocardiogram (ECG) and echocardiogram (ECHO) profiles of screened athletes.

ECG Data				
	Female (n=11)	Male (n=30)	All athletes (n=41)	p-value
HR (bpm)	63.4	65.4	64.9	0.644
PR (ms)	165.5	163.9	164.3	0.855
QRS (ms)	90.0	98.2	96.0	0.004
QT (ms)	397.1	396.3	396.5	0.941
QTc (ms)	404.7	408.4	407.4	0.690
Normal sinus rhythm	54.5% (6)	60.0% (18)	58.5% (24)	0.753
Sinus bradycardia	45.5% (5)	30.0% (9)	34.1% (14)	0.355
1° heart block	0.0% (0)	13.3% (4)	9.8% (4)	0.202
Axis deviation	18.2% (2)	10.0% (3)	12.2% (5)	0.478
J-Point elevation	18.2% (2)	53.3% (16)	43.9% (18)	0.044
T-Wave inversion	36.4% (4)	40.0% (12)	39.0% (16)	0.832
ST-Segment depression	0.0% (0)	3.3% (1)	2.4% (1)	0.540
ST-Segment elevation	0.0% (0)	16.7% (5)	12.2% (5)	0.149
Left atrial enlargement	0.0% (0)	10.0% (3)	7.3% (3)	0.276
Right atrial enlargement	9.1% (1)	10.0% (3)	9.8% (4)	0.931
Right ventricle hypertrophy	9.1% (1)	13.3% (4)	12.2% (5)	0.713
Complete LBBB	0% (0)	0% (0)	0% (0)	NA
Complete RBBB	0.0% (0)	3.3% (1)	2.4% (1)	0.540
Incomplete RBBB	9.1% (1)	6.7% (2)	7.3% (3)	0.792
Incomplete LBBB	0% (0)	0% (0)	0% (0)	NA
Ventricular pre-excitation	0% (0)	0% (0)	0% (0)	NA
Pathological Q waves	0.0% (0)	10.0% (3)	7.3% (3)	0.276
>2 PVC per 10 seconds	0% (0)	0% (0)	0% (0)	NA
Ultrasound Measurement Data				
Inner left ventricular diameter (cm)	4.9	5.2	5.1	0.219
Interventricular septal wall thickness (cm)	0.8	1.0	0.9	0.002
Posterior wall thickness (cm)	0.8	1.1	1.0	<0.001
Aortic root breadth (cm)*	2.3	2.7	2.6	0.002

HR, heart rate; *bpm*, beats per minute; *ms*, milliseconds; *LBBB*, left bundle branch block; *RBBB*, right bundle branch block; *PVC*, premature ventricular contractions; *cm*, centimeters.

Logistically, all aspects of the study can be completed simultaneously due to this coordination of care teams and necessary equipment. Second, our athletic department policy dictates that all athletes obtain at minimum a H and P and ECG upon matriculation. Thus, the addition of a cardiac ultrasound, if kept to a minimum time requirement, is minimally disruptive to routine screening procedures. Third, available ultrasound equipment within a Sports Medicine department can help to minimize costs of this study and avoid logistical errors when obtaining a machine. Fourth, having a cardiologist present for the screenings is coordinated by our athletic department and set as standard of care. When considering the potential of using point of care bedside ultrasound as a screening technique, it is reasonable to consider using other trained providers to obtain these images, whether they are emergency medicine and ultrasound trained physicians or sonographers, the personnel can be varied. Thus, the task of coordinating an additional busy physician's schedule to oversee the exam is mitigated. Thus, the preexisting standard of care for athletes at an institution is the largest facet to making this study, and addition of point of care cardiac ultrasound at any institution, feasible.

LIMITATIONS

There are several limitations to this study. Patients were enrolled using a convenience sample and our data is therefore subject to sample bias. All athletes were unable to be represented

in the study. Some were not available due to class interference, practice obligations, or leaving before research coordinator contact. Regarding medical history, information provided was limited to the participant's knowledge of family and personal medical history. Family members with high risk histories were potentially omitted by student-athletes due to lack of knowledge or unwillingness to volunteer the information. We did not screen for any coronary artery abnormalities although this could be another cause of cardiac disease in young athletes. Our sample size was small and it is unclear if our findings can be generalized to the population. Future large-scale studies are needed to validate our findings. Based on the statistical prevalence of hypertrophic cardiomyopathy and other structural or congenital heart defects, this requires a much larger sample size to understand the utility of point of care cardiac ultrasound in detection of these conditions.

CONCLUSION

Our study demonstrates the feasibility of a hypertrophic cardiomyopathy screening program that includes H and P, ECG and point of care ultrasound. We did not detect any cases of HCM in this small sample size. However, we believe that adding point of care ultrasound to the preparticipation exam is feasible. This workflow may provide a model for other athletic departments' screening routines. This model could also serve cost-analysis studies for adding the ultrasound to routine protocols. Future large-scale studies are needed to validate our promising findings.

ACKNOWLEDGEMENTS

We would like to recognize the assistance of the following individuals: Hap Zarzour, our statistician Dr. Maragatha Kuchibhatla and the many other athletic trainers and physicians involved with the continued care of our student athletes.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Physician Documentation of Access to Firearms in Suicidal Patients in the Emergency Department

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Section Editor: Wirachin Hoonpongsimanont, MD, MS
Submission history: Submitted February 6, 2019; Revision received May 11, 2019; Accepted July 4, 2019
Electronically published August 20, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.4678

Introduction: Suicide is the 10th leading cause of death in the United States. An estimated 50% of these deaths are due to firearms. Suicidal ideation (SI) is a common complaint presenting to the emergency department (ED). Despite these facts, provider documentation on access to lethal means is lacking. Our primary aim was to quantify documentation of access to firearms in patients presenting to the ED with a chief complaint of SI.

Methods: This was a cross-sectional study of consecutive patients, nearly all of whom presented to an academic, urban ED with SI during July 2014. We collected data from all provider documentation in the electronic health record. Primary outcome assessed was whether the emergency physician (EP) team documented access to firearms. Secondary outcomes included demographic information, preexisting psychiatric diagnoses, and disposition.

Results: We reviewed 100 patient charts. The median age of patients was 38 years. The majority of patients had a psychiatric condition. EPs documented access to firearms in only 3% of patient charts.

Conclusion: EPs do not adequately document access to firearms in patients with SI. There is a clear need for educational initiatives regarding risk-factor assessment and counseling against lethal means in this patient cohort. [West J Emerg Med. 2019;20(5)818-821.]

INTRODUCTION

Firearm-related injury and death is a significant and expensive public health issue. Recent data from the Centers for Disease Control and Prevention (CDC) report suicide as the 10th leading cause of death in the United States, with firearms reported as the cause of death in an estimated 50% of these cases.[1] Additionally, the direct medical costs related to firearm injuries nationally are as high as $2.9 billion dollars per year.[2]

Firearm injuries are also a common reason patients present to the emergency department (ED). ED visits for firearm injuries occurred at an estimated national incidence of 25.3 ED visits per 100,000 people between 2006 and 2014; the burden of non-fatal firearm injuries is likely underestimated at 2.4 times that of fatal injuries.[2] Given the magnitude of firearm-related injury and death in the U.S., there is a clear public health need for educational initiatives and patient-centered interventions regarding firearm safety.

Additionally, the ED is a frequent point of access to care for patients with suicidal ideation (SI).

Previous work demonstrated that many patients have their first point of contact with the mental healthcare system less than one month before suicide is attempted, and that disadvantaged groups are less likely to have access to outpatient mental healthcare.[3] For this reason, many people present to EDs in times of suicidal crisis. In 2013 the Agency for Healthcare Research and Quality found that 903,400 ED visits were related to SI; this constitutes an estimated 12% average annual increase in the population-based rate of ED visits for SI since 2006.[4] Survey data from 9708 individuals suggested 64% of patients with SI and 79% of patients with suicide attempt sought general medical or subspecialty care in the year prior to presentation.[5]

However, only 44% of those patients with SI sought mental health treatment during that time.[5]

In evaluation of healthcare providers' perception of responsibility when it comes to the assessment of access to firearms, a Betz et al. survey of ED providers revealed that only 43% believed that "'most' or 'all' suicides are preventable."[6] Another study noted that 57% of ED nurses and physicians believed it was the responsibility of the ED nurse to ask about access to firearms, and 71% felt that it was the emergency physician's (EP).[7] However, in this study,84% of respondents felt that it was the responsibility of the psychiatrist to ask patients about their access to firearms.

Given these beliefs, some skepticism exists about the EP's role in risk assessment of lethal-means access in suicidal patients. In subsequent work, Betz et al. found low rates of EP documentation of access to lethal means in suicidal patients.[8] However, no clear documentation guidelines exist for emergency providers on risk assessment in such situations. Without clear documentation in the electronic health record (EHR), it is difficult to know whether emergency providers are asking these patients about access to firearms.

Objectives

The goal of this study was to quantify provider documentation of access to firearms in patients who present to the ED with a chief complaint of SI. We hypothesized that EPs did not consistently document access to firearms in patients presenting with SI. Our secondary outcomes were to assess demographic information, preexisting psychiatric diagnoses, and disposition in this cohort.

METHODS

Study Design and Setting

This was a cross-sectional study of consecutive patients presenting to the ED with SI. The study sites included two EDs; the first is an urban, academic, tertiary-care referral center with approximately 95,000 ED visits per year, and the second is an affiliated community hospital with approximately 11,500 ED visits per year. Patients presenting to these EDs with SI are cared for by attending EPs and resident physicians in emergency medicine and psychiatry. This observational study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies.[9] This study was approved by the institutional review board (IRB).

Selection Criteria

We reviewed the medical records of consecutive patients who presented to an ED between July 1, 2014, and July 31, 2014, with a nursing triage chief complaint of SI. This brief study period was used as a needs assessment in the development of a subsequent, prospective, ED-based quality improvement program on counseling on access to lethal means. Patients with multiple ED presentations during the study period were included once at the time of their index visit.

Variables

We collected data on the following variables: age; sex (male, female); race (African American, Caucasian, other); marital status (married, single, romantic partner, unknown); psychiatric diagnosis (anxiety, bipolar, depression, psychosis not otherwise specified, schizophrenia, other, none); disposition (admit, discharge, transfer); and whether there was EP documentation of patient access to firearms in this cohort.

Data Sources

We identified patient encounters through query of the EHR for ED patients presenting with a chief complaint of SI. These data were stored on a password-protected secure server in compliance with our institution's IRB. Data were queried by S.N. from the entire ED chart including EP documentation, nursing documentation, psychiatry consult notes, and pre-hospital documentation in the EHR.

Analysis

We presented the data as descriptive statistics. Categorical data is presented in both raw count and percentages.

RESULTS

Of the total 100 patient encounters included in our study, 99 of these patients presented to the academic center, and one presented to the community ED. We excluded eight patient encounters for repeat visits during the study period, and one was excluded for a complaint that was not related to SI or mental health. Patient characteristics are described in the Table. The median age was 38 years. Of those patients presenting to the ED for SI, 64% were male and 53% were Caucasian; 54% were single, and 13% were married. The majority of patients had an underlying psychiatric diagnosis. Nearly equal thirds of patients were admitted, transferred to other psychiatric hospitals for admission, and discharged.

We found that EPs documented access to firearms in only 3% of the study population; 97% of these patient encounters did not contain documentation of access to firearms (Figure). Of the 100 patients queried, psychiatry was consulted on 81 patients;78% of these patients had access to firearms assessment documented by the psychiatry consultant.

DISCUSSION

We found that EPs did not routinely document access to firearms in suicidal patients. Of particular concern, this discussion of access to firearms—the most common method of completed suicide in the U.S.—was not documented by EPs in 97% of patients. These findings support

Table. Demographics and characteristics of 100 patients who presented to the emergency department with suicidal ideation between July 1–July 31, 2014.

Age, number	
Age, median (IQR)	38 (26 – 47)
Age range	19 – 68
Sex, number	
Male	64
Female	36
Race, number	
African American	43
Caucasian	53
Other	4
Marital status, number	
Married	13
Partner	12
Single	54
Unknown	21
Psychiatric diagnoses, numer	
Anxiety	13
Bipolar	29
Depression	48
None	9
Psychosis, not otherwise specified	7
Schizophrenia	21
Other*	39
Disposition, number	
Admit	32
Discharge	32
Transfer	36

*Includes personality disorders, attention-deficit/hyperactivity disorder, and substance-induced mood disorders.
IQR, interquartile range.

previous work that indicate physicians in general, and EPs specifically, are not asking suicidal patients about their access to firearms.[8] Although the psychiatry consultants had improved documentation rates of patient firearm access in this cohort, they too had a significant gap, with firearm access documentation absent in 22% of psychiatry consult notes. Ultimately, EPs are responsible for all aspects of ED care and it is important for EPs, specifically, to document this risk factor.

While the sample size and time period for this study were small, the marked lack of EP documentation on this issue was the wake-up call needed to launch a prospective, ED-based quality improvement program on counseling on access to lethal means in patients presenting with SI. As firearms are the most common way that Americans die by suicide, we submit these data for consideration with the hope that similar brief analyses at other institutions will improve discussion, documentation, and ED-based counseling on access to, and safe storage of, firearms and other lethal means in ED patients at times of suicidal crisis.

LIMITATIONS

This study was limited by its retrospective design and small sample size, and no statistical software was required for the analysis. Of note, primary endpoints for this study were limited by provider documentation in the EHR; it is possible that more physicians had discussed access to lethal means with their patients and did not document these conversations.

CONCLUSION

The ED is uniquely positioned to evaluate for and disseminate information regarding access to and safe storage of firearms at times of suicidal crisis. As lethal means counseling is a core practice guideline in suicide risk assessment and management, the Suicide Prevention Resource Center designed an online training module, Counseling on Access to Lethal Means (CALM), to train healthcare providers on how to counsel patients at risk of suicide on their access to lethal means, such as firearms.[10,11] This training module also discusses strategies for safe storage of lethal means during times of suicidal crisis. In response to our findings, we have used these resources to implement a bedside CALM quality improvement initiative in our academic center ED for suicidal patients and their family members.

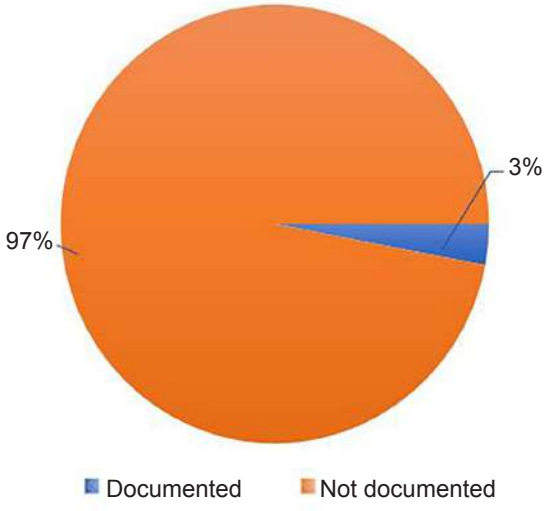

Figure. Emergency physician documentation of firearm access in 100 patients who presented to the emergency department for suicidal ideation between July 1–July 31, 2014.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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Sepsis in Pregnancy: Recognition and Resuscitation

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Section Editor: Gabriel Wardi, MD
Submission history: Submitted April 9, 2019; Revision received May 23, 2019; Accepted June 16, 2019
Electronically published August 6, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.6.43369

The normal physiologic changes of pregnancy complicate evaluation for sepsis and subsequent management. Previous sepsis studies have specifically excluded pregnant patients. This narrative review evaluates the presentation, scoring systems for risk stratification, diagnosis, and management of sepsis in pregnancy. Sepsis is potentially fatal, but literature for the evaluation and treatment of this condition in pregnancy is scarce. While the definition and considerations of sepsis have changed with large, randomized controlled trials, pregnancy has consistently been among the exclusion criteria. The two pregnancy-specific sepsis scoring systems, the modified obstetric early warning scoring system (MOEWS) and Sepsis in Obstetrics Score (SOS), present a number of limitations for application in the emergency department (ED) setting. Methods of generation and subsequently limited validation leave significant gaps in identification of septic pregnant patients. Management requires consideration of a variety of sources in the septic pregnant patient. The underlying physiologic nature of pregnancy also highlights the need to individualize resuscitation and critical care efforts in this unique patient population. Pregnant septic patients require specific considerations and treatment goals to provide optimal care for this particular population. Guidelines and scoring systems currently exist, but further studies are required. [West J Emerg Med. 2019;20(5)822-832.]

INTRODUCTION

In the United States, sepsis is the fourth leading cause of maternal death.[1-3] Mortality in pregnant patients rose consistently at an average of 9% per year from 2001 to 2010 despite sepsis guidelines updates.[1,4,5] As sepsis occurs in only 0.001% of pregnancies and in 0.002-0.01% of postpartum patients, data and consensus are limited regarding diagnostic and therapeutic interventions.[4] Additionally, pregnancy is an exclusion criterion in all major sepsis trials to date, relinquishing clinical decisions to provider preference and expert opinion.[6-8]

METHODS

In the following narrative review, we sought to comprehensively review the recent literature regarding sepsis in pregnancy. While pregnancy has been an exclusion criterion in every major sepsis trial as well as disease-specific trials, we identified all major observational trials, retrospective cohort studies for clinical rule derivation, and their subsequent validation studies.[6-8] We also searched PubMed and Google Scholar from 1966 to October 2018 for English-language articles using a combination of keywords and medical subject headings "pregnancy" and "sepsis" for production of this narrative review, including case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, narrative reviews, and clinical guidelines. Three authors decided which studies to include for the review by consensus, with 122 resources selected for inclusion, focusing on ED evaluation and management. This review also highlights areas where more research is needed and underscores the protean nature of this complex physiology. As this is a narrative review and not a systematic review and/or meta-analysis, we did not grade the included resources or pool data.

DISCUSSION

The Pregnant Body: Shifting Homeostasis

The altered physiology of pregnancy can affect the immunologic response and clinical presentation of sepsis. Clinicians must be vigilant of the potentially competing priorities

of mother and fetus, as physiologic changes brought on by sepsis in pregnancy in the mother can generate untoward effects on the fetus. It is essential to understand physiologic changes of normal pregnancy to appropriately approach sepsis in pregnancy. These changes occur secondary to altered hormonal levels that continue from conception to post-delivery, as well as anatomic transformations with fetal growth and uterine enlargement.[9]

Normal changes in pregnancy include a relative anemia due to expanding plasma volume that outpaces red blood cell growth.[10] A baseline respiratory alkalosis develops from a rise in respiratory tidal volume with increased minute ventilation.[11] Specific gastrointestinal differences likewise affect both normal baseline and disease resuscitation. The gravid uterus increases intragastric pressures, and high levels of progesterone and relaxin decrease lower esophageal sphincter tone.[12,13] A normal delay in gastric emptying and elevation of the diaphragm up to four centimeters (cm) increase aspiration risk, elevating the risk of aspiration pneumonia and complicating intubating conditions.[14]

Throughout pregnancy the cardiovascular system undergoes a multitude of changes contributing to the physiology of mother and fetus. Systemic vasodilation begins early in the first trimester, decreasing systemic vascular resistance (SVR) by up to 35-40%, maintaining cardiac output due to a compensatory increase in heart rate.[15] Late in the third trimester, heart rate peaks at rates up to 24% higher than the prepartum baseline.[15,16] This translates to heart rate increases up to 30 beats per minute.[17-19] Multiple gestations can further increase maternal heart rates.[20] These compensatory cardiovascular changes generally return to baseline within two weeks of delivery, although a small proportion of patients maintain their pregnant cardiovascular measures at 12 weeks postpartum.[9,21] Blood pressure may fall by 10-15 millimeters of mercury (mm Hg) in a normal pregnancy and nadir around 24 weeks gestation.[18,21,22] Expanding plasma volume and red blood cell mass further work to offset lowered SVR and to maintain normotension from as early as six weeks into pregnancy until 34 weeks gestation.[19]

Pregnancy alone can increase white blood cell (WBC) counts to double pregestational levels.[23] WBC counts may reach levels as high as 25,000 cubic millimeters (mm^3) in a normal pregnancy.[24-27] The physiologic stress of the peripartum period can push this leukocytosis further as high as 25,000/mm^3 immediately postpartum.[24] WBC counts may rise even higher in pre-eclampsia, complicating laboratory data interpretation.[28,29] A clinical suspicion for pre-eclampsia taken with immunologic changes may cloud an infectious differential.[30] Further normal physiologic changes in pregnancy are highlighted in Table 1.

Other pre-existing comorbidities may complicate physiologic alterations of pregnancy. Long-term medication use in pregnancy has increased commensurately with rates of obesity, non-insulin dependent diabetes mellitus, and hypertension.[31,32] Prescription medication use during pregnancy has increased as much as 60% over the last 30-40 years.[33] In the setting of infection, medications targeting blood pressure and glucose control can obscure physiologic responses. Non- or poorly-compliant pregnant patients further complicate this already-cloudy picture.

The Evolution of Sepsis: Issues with Diagnosis and Guidance

The definition of sepsis continues to evolve. Previously,

Table 1. Physiologic changes during pregnancy.[4]

System	Baseline Changes	Physiologic Impact
Cardiovascular	Decreased arterial pressure Increased heart rate and cardiac output	Increased risk of hypoperfusion in sepsis Abnormal baseline may mask signs of sepsis
Gastrointestinal	Decreased esophageal tone and delayed gastric emptying	Aspiration pneumonia risk Increased aspiration risk with airway interventions
Genitourinary	Decreased vaginal pH	Increased risk of chorioamnionitis
Hematology	Increased plasma volume without proportional increase in red cell mass, hemoglobin Increased production of factors VII, VIII, IX, X, XII and von Willebrand factor	Physiologic anemia, decreased O_2 supply to tissues Increased risk of disseminated intravascular coagulation and venous thromboembolic disease
Respiratory	Increased tidal volume and minute ventilation with typically unchanged respiratory rate Decreased residual volume due to elevated diaphragm	Decreased $PaCO_2$ levels (A"normal" blood gas may therefore reflect impending respiratory failure.) Decreased oxygenation with faster rate of desaturation
Renal	Ureteral dilation and increased vesicoureteral reflux Increased renal plasma flow and glomerular filtration rate	Increased risk of pyelonephritis Abnormal baseline may mask renal injury in sepsis

$PaCO_2$, partial pressure of carbon dioxide.

suspected infection source in conjunction with systemic inflammatory response syndrome (SIRS) criteria was key to identification[34] Although these studies excluded pregnant patients, SIRS criteria nevertheless remained the primary standardized assessment tool for sepsis recognition.[34] Before the second update to the sepsis guidelines in 2012, guidelines did not accurately identify maternal sepsis, identifying less than two-thirds of obstetric patients in retrospective reviews, highlighting the need to delineate pregnancy-specific guidelines.[3,35]

Working in parallel to the Surviving Sepsis Campaign, other parties presented criteria aimed at identifying maternal sepsis. The World Health Organization (WHO) modified the definition of maternal sepsis to "puerperal sepsis."[36] This narrow definition limited pregnant or postpartum sepsis to genitourinary tract infections between the time of rupture of membranes and six-weeks postpartum.[37,38] The WHO provided a definition for septic abortion, which likewise remained isolated to genitourinary tract infections.[36,38] As a result, many early maternal sepsis studies focused solely on the diagnosis and treatment of only these infections.[39-45]

Diagnoses were most recently supplemented in the Third International Consensus Definitions for sepsis and septic shock in 2016 by the Sepsis-related Organ Failure Assessment (SOFA) and the quick Sepsis-related Organ Failure Assessment (qSOFA) using SIRS criteria as fundamental principles.[46,47] Similar to preceding trials, pregnancy was an exclusion criterion in these studies that established and validated the SOFA and qSOFA scores, thereby minimizing their utility in the pregnant population.[46,47] As of this review, no studies have externally validating SOFA or qSOFA scores in pregnant patients, despite the fact that the components of these scores have been validated in various combinations in pregnant populations.[37]

The creation of two scores, the modified early warning scoring systems (MOEWS) and the sepsis in obstetrics (SOS) score, attempted to stratify pregnant patients with concern for sepsis; however, attempts to validate these scores have generated varying utility.[35,48] MOEWS has a number of international variants (Table 2), limiting its application across regions and settings. MOEWS is generally hindered by its outcome "to help detect the early signs of illness and trigger timely medical review with appropriate intervention," rather than specifically to target sepsis identification.[49] The lone major MOEWS validation study analyzed 913 cases of chorioamnionitis, but only five cases met the definition of severe sepsis.[48] Intended to predict severe sepsis by 2.0 guidelines, MOEWS restricts its utility not only by using a recently redefined term, but also by generating a myopic view of sepsis in pregnancy by focusing on chorioamnionitis and not the broader scope of sepsis sources.[49]

In 2014 the SOS sought to establish an obstetric-focused scoring system, incorporating the previously highlighted physiological changes in the cardiovascular, respiratory, and immune systems in pregnancy (Table 3).[50] Based on the surviving sepsis campaign, the SIRS criteria overestimated morbidity and mortality in an obstetric cohort without accounting for normal physiologic changes.[51-55] With this tailored scoring system, the authors sought to identify pregnant patients at high risk for sepsis with a primary outcome of intensive care unit (ICU) admission within 48 hours of admission. However, ICU admission criteria were not standardized.

Most recently, a single, prospective, internal validation trial of the SOS attempted to evaluate its performance with the same primary outcome.[56] An SOS score of less than six points had a 64% sensitivity and 98.6% negative predictive value for excluding sepsis, although a score of six points or greater had a sensitivity of only 64% to diagnosis sepsis.[56] Furthermore, of the 1250 pregnant patients presenting to the ED over a three-year study period, only 1.1% were admitted to the ICU, although ICU admission criteria remain unknown.[56] While this lone, prospective validation study demonstrates a significant negative predictive value, additional validation studies and a larger sample population are needed to determine its utility in populations with different prevalence of septic pregnant patients.

Despite the need for obstetric-focused scoring systems in sepsis, emergency providers lack substantially validated criteria or schema to bolster decision-making and hospital admission when confronted with a sick pregnant or postpartum patient.

Table 2. Versions of the modified obstetric early warning scoring systems (aggregate score MOEWS).[35]

Variable	Low abnormal range			Normal	High abnormal range			
Score	3	2	1	0	1	2	3	Trigger
Heart rate	≤39	40-59	60-74	75-104	105-109	110-129	≥130	
Systolic blood pressure	≤79		80-89	90-139	140-149	150-199	≥200	Medium Risk: Score 4-5
Respiratory rate	≤5	5-9	10-14	15-19	20-24	25-29	≥30	
Temperature	≤34.9		35-35.9	36.0-37.9	38.0-38.4		≥38.5	High Risk: Score[3] 6
Oxygen saturation	≤87	88-89	90-94	95-100				
Mental status				Alert	Voice	Pain	Unresponsive	

Table 3. The Sepsis in Obstetrics Score (SOS) scoring criteria.[58]

Variable	Low abnormal range				Normal		High abnormal range		
Score	4	3	2	1	0	1	2	3	4
Heart rate					≤119	120-129	130-149	150-179	≥179
Systolic blood pressure	<70		70-90		>90				
Respiratory rate	≤5		6-9	10-11	12-24	25-34		35-49	>49
Temperature		≤34.9		35-35.9	36.0-37.9	38-38.4		≥38.5	High Risk Score ≥ 6
Oxygen saturation	≤85%	85-89%		90-91%	≥92%				
White blood cell count	<1		1-2.9	3-5.6	5.7-16.9	17-24.9	25-39.9		>39.9
% Bands					<10%		≥10%		
Lactic acid					<4		≥4		

Treatment Considerations Specific to Pregnancy

Pneumonia

Pneumonia is responsible for 30% of infections in pregnant patients with severe sepsis, carrying significant morbidity for both mother and fetus.[5] In one study, up to one-fifth of pregnant patients experienced a delay in pneumonia diagnosis, while half experienced significant morbidities such as empyema and respiratory failure.[57] Initial diagnosis is often made by chest radiograph. Appropriate shielding of the abdomen exposes the fetus to less than 0.01 milliGray (mGy), well below the threshold of adverse effects.[58] The lung may be upwardly displaced by the growing uterus, and the increased density of parenchyma can make definitive diagnosis difficult.[59] Ultrasound (US) has a 94-97% sensitivity and 94-96% specificity for pneumonia diagnosis in a recent meta-analysis.[59,60] Although chest computed tomography (CT) is rarely required, it can be safely performed if needed for diagnosis.[46]

The most common microbial causes of pneumonia in pregnancy include *S. pneumoniae* and *H. influenzae*.[61] Antibiotic coverage should treat these pathogens. However, other sources to consider include *Legionella* spp., Varicella zoster, and *Pneumocystis jirovecii* in patients with human immunodeficiency virus (HIV).[13] While fluoroquinolones should be avoided, penicillins, cephalosporins, and macrolides are all considered safe to use in pregnancy.[62] For pregnant patients admitted to the ICU, both *S. pneumoniae* and *Legionella* spp. should be covered.[62] A pneumococcal beta lactam, such as cefotaxime or, if not peripartum, ceftriaxone, and a macrolide should be administered.[13,62] Vancomycin and linezolid do not currently have established safety in pregnancy, but should be considered in cases where methicillin-resistant *Staphylococcus aureus* is suspected.

In a small case series, 59% of pregnant patients with pneumocystis pneumonia required mechanical ventilation due to respiratory failure.[63] The authors found a 50% mortality rate for the mothers and 41% mortality for combined fetus and neonates.[63] These patients should be treated similarly to their non-pregnant counterparts with trimethoprim-sulfamethoxazole and corticosteroids if the A-a gradient is greater than 35 or the partial pressure of oxygen (PaO_2) is less than 70 mm Hg.[64] The mother should also be monitored for immune reconstitution inflammatory syndrome .[64] If treatment is active at the time of delivery, the neonate should be monitored for hyperbilirubinemia.[64]

The course of pneumonia in pregnant patients can be further complicated by decreased secretion clearance and worsening airway obstruction.[13,61] Secondary to pregnancy physiology and treatments routinely administered in the course of delivery, aspiration during labor represents another significant source of infection.[14] Epidural blocks may blunt or inhibit the cough reflex, further increasing the risk of aspiration pneumonitis and pneumonia.[65]

Pregnancy was an exclusion criteria in the PROTECT (prophylaxis for thromboembolism in critical care) trial, which examined risk factors for mortality secondary to pneumonia in patients admitted to the ICU.[66] ICU admission threshold should be lower for pregnant individuals, as they have decreased tolerance for hypoxemia and may quickly deteriorate with pneumonia.[13] Blood gas interpretation in pregnant patients should take into account the expected physiologic alkalemia, which may blunt initial laboratory findings of hypercapneic respiratory failure.[14] Anatomical compression of the inferior vena cava in late pregnancy can reduce cardiac preload causing hypotension, exacerbated by the addition of positive pressure from mechanical ventilation.[11,24] This may necessitate placing the patient in the left lateral decubitus position.[67] Prevention of maternal hypoxemia is critical, as this quickly leads to fetal decompensation. Thus, maintaining a PaO_2 greater than 70 mm Hg can prevent deleterious effects on the fetus.[68,69] Although extrapolated from

asthma data and therefore controversial, partial pressure of carbon dioxide should be maintained between 28-32 mm Hg to prevent fetal acidemia and maternal hypercapnia.[69]

Pyelonephritis

Pyelonephritis in pregnancy is a complicated infection requiring intravenous (IV) antibiotics and admission for continued monitoring of mother and fetus.[70,71] Pyelonephritis occurs in approximately 2% of pregnancies in the U.S. but accounts for the largest proportion of maternal inpatient admissions.[71] Up to 20% of cases occur in the second and third trimester.[70-72] Numerous factors predispose pregnant women to pyelonephritis: dilation of the renal calyces secondary to progesterone; stagnation of ureteral peristalsis; mechanical compression of the bladder; and increased glomerular filtration rate, resulting in glucosuria and alkaluria facilitating bacterial growth.[73]

Acute pyelonephritis in pregnancy can significantly increase the risk of maternal anemia, acute renal failure, respiratory distress, and preterm birth.[4] Additionally, patients with maternal pyelonephritis demonstrate a 33% increased risk of chorioamnionitis, further predisposing them to sepsis.[74] More than 80% of acute pyelonephritis cases in pregnancy are from *E coli*, but other uropathogens include *Klebsiella, Streptococcal* spp*., Proteus mirabilis,* and *Enterococcus*.[74,75] Although pregnant patients are specifically excluded from Infectious Diseases Society of America (IDSA) guidelines, ceftriaxone, cefepime, or ampicillin plus gentamicin are feasible treatment options.[74,75] In patients less than 24 weeks gestation, intramuscular ceftriaxone has demonstrated equal efficacy in length of hospitalization and days until resolution of infection compared to IV ampicillin and gentamicin or cefazolin.[76] Ceftriaxone should be avoided in the periparturition period, however, due to the risk of neonatal kernicterus.[67] Urine culture and local resistance patterns should guide empiric therapy.[73]

Carbapenems or piperacillin-tazobactam could be considered for broader coverage in immunocompromised patients or those with severe pyelonephritis impairing urinary drainage; however, imipenem should be avoided due to adverse fetal effects demonstrated in vivo.[70,73] *E. coli* and other gram-negative rods cause the vast majority of pyelonephritis in pregnancy, carrying the potential for large-scale endothelial cell damage in capillary beds from endotoxin release.[73-75] This endothelial damage commonly affects renal and pulmonary tissue, resulting in acute respiratory distress syndrome in 1-8% of cases, further complicating the maternal patient.[73] Unlike the non-pregnant population, a test of cure is required in maternal patients following clinical resolution.[67]

Appendicitis

Appendicitis occurs less frequently in pregnancy (approximately 1 in 1500) and peaks in the second trimester compared to the non-pregnant population.[77-79] However, 1 in 1000 pregnancies undergo surgical evaluation for possible appendicitis, with increased rates of surgical intervention due to increased perforation risk as well as mortality.[77,78] Maternal mortality secondary to appendicitis is 4%, and complications of perforated appendicitis result in an estimated 43% fetal mortality rate.[80,81]

Physiologic changes of pregnancy and atypical presentation make maternal diagnosis particularly challenging. The fundus rises and displaces the appendix from the right lower quadrant (RLQ).[81] Fundal displacement of the omentum prevents it from sealing off an inflamed appendix.[82] RLQ pain and tenderness are the presenting symptoms in 75% of maternal appendicitis, while another 20% of cases present with right upper quadrant pain.[83] However, up to 45% of these cases present with rectal tenderness, which is not commonly associated with or examined with suspected appendicitis.[83] Nausea and vomiting, common in pregnancy, can further complicate the clinical picture. Therefore clinicians should note any significant changes to the patient's "normal" course of "morning sickness" during the history. Maternal leukocytosis is not reliable for diagnosing appendicitis or perforation due to normal physiologic changes. However, the presence of bilirubinemia greater than 1.0 milligrams per deciliter (mg/dL) has demonstrated sensitivity of 70% and specificity of 86% in evaluating for perforation in appendicitis, which may aid clinical judgment.[84]

While ultrasound (US) is safe in pregnancy, wide variation in appendiceal location makes evaluation difficult. Sensitivity and specificity of US for the diagnosis of maternal appendicitis ranges from 67-100% and 83-95%, respectively.[85] The lower range is significantly less compared to non-pregnant populations in ED-performed bedside US, where sensitivity and specificity approximate 49.5-86.2% and 91.4-99.7%, respectively.[86] In cases where US is equivocal, magnetic resonance imaging (MRI) is recommended, sparing ionizing radiation to both mother and fetus.[87] A meta-analysis of MRI in the diagnosis of maternal appendicitis demonstrated a sensitivity of 96.8% and a specificity of 99.2%.[88]

MRIs are routinely run without gadolinium, which poses no hypothetical risk to the fetus.[87] Early antibiotic coverage should be initiated with a second-generation cephalosporin and clindamycin or metronidazole.[89] Prompt surgical consultation should be obtained, as the risk of perforation rises with delaying surgical involvement for more than 24 hours.[89,90] Additionally, the risk of fetal loss increases with perforation of the appendix, with a 36% rate of fetal loss, compared to 1.5% without appendiceal rupture, underscoring the importance of early surgical consult in conjunction with antibiotics.[91]

Pelvic Inflammatory Disease

Although rare, maternal sepsis from pelvic inflammatory disease (PID) is associated with high-mortality for mother and fetus, as well as increased risk of preterm delivery.[92] PID in pregnancy presents typically in the first trimester with fever and abdominal pain, adnexal tenderness, and cervical motion tenderness. Bacteria can ascend prior to the mucus plug sealing off the decidua around 12 weeks.[93] PID may rapidly progress to

tubo-ovarian abscess (TOA), with a mortality up to 9%.[94] TOA presents similarly to an infected ectopic pregnancy with fever and adnexal tenderness. The presentation of fever, leukocytosis, and diarrhea should prompt consideration of TOA, independently predicted by elevated C-reactive protein.[95] Pregnancy with PID requires hospitalization for treatment.[92] Doxycycline, the mainstay treatment for PID per IDSA guidelines, has been repeatedly proven to have severe teratogenicity and therefore should not be used.[92] Azithromycin should be substituted, in conjunction with an IV second-generation cephalosporin such as cefotetan or cefoxitin.[92] Penicillin cross-reactivity with second-generation cephalosporins is negligible, providing effective treatment in pencillin-allergic patients.[96,97] This regimen also covers *Mycoplasma genitalium*, which accounts for up to 8.7% of non-chlamydial and non-gonococcal PID cases.[98]

Endometritis

Endometritis presents with postpartum fever, tachycardia, and foul lochia or malodorous vaginal discharge and occurs with ascension of bacteria during labor that colonizes amniotic fluid and decidua.[67] Cases are generally polymicrobial, with two-thirds containing both anaerobic (Bacteroides, Clostridium, and Peptostreptococcus spp.) and aerobic bacteria (Group B Streptococcus, E. coli, and enterococcus).[99] The presence of a hematoma is concerning for S. pyogenes and S. aureus and toxic shock syndrome.[77] IV gentamicin and clindamycin are efficacious, although this regimen does not cover enterococcus.[100] Doxycycline plus cefoxitin or ampicillin/sulbactam is an additional regimen. In those who do not respond within the first 48-72 hours, ampicillin is added to cover for these pathogens.[101] In patients delivering via cesarean section (C-section) who develop endometritis, parametrial cellulitis with phlegmon formation in the broad ligament or, less-commonly, parametrial phlegmon can cause persistent fevers and require interventional radiology consult for drainage.[101] Venous drainage post-C-section can also spread infection, generating septic pelvic thrombophlebitis.[102]

Pelvic thrombophlebitis is usually refractory to broad-spectrum antibiotics alone and requires anticoagulation with broad polymicrobial coverage.[102–104] Liberal use of postpartum CT has significantly impacted management. In a retrospective cohort study of 238 postpartum patients, the use of CT resulted in alteration of antibiotic therapy in 10%, addition of low-molecular weight heparin (LMWH) in 12%, and surgical intervention in 17%.[105] This study demonstrated that the addition of CT significantly impacted the clinical course of approximately 40% of patients.[105] Table 4 summarizes these infections.

Approach to Resuscitation in Pregnancy

Optimal stabilization of the fetus depends on adequate resuscitation of the mother.[77] Initial resuscitation should include IV fluid administration and optimized positioning. The left lateral decubitus position maximizes patient hemodynamics in the third trimester, improving preload by decreasing inferior vena cava compression.[77] Fluid resuscitation should begin within the first three hours of presentation with an initial recommended volume of 30 milliters per kilogram of crystalloid if either hypotension or lactic acid >4 millimoles per liter (mmol/L) is present.[107] Due to increased blood volume in pregnancy, a lactic acid threshold of 4 mmol/L may lack sensitivity in this population. In a retrospective cohort of 159 septic pregnant patients, the mean lactic acid level of those admitted for ICU level care was 2.6 mmol/L, and those

Table 4. Chronologic presentation of sepsis etiologies and recommended antibiotics.

Infection	Time Frame	Evaluation	Management
Pelvic inflammatory disease	1st trimester	Pelvic examination, transvaginal ultrasound to evaluate for tubo-ovarian abscess if suspected[93–95]	Azithromycin and cefoxitin[92]
Appendicitis	2nd trimester more commonly than 1st and 3rd trimester	Ultrasound, if equivocal then magnetic resonance imaging	Definitive treatment is surgery, cefoxitin + clindamycin, cefoxitin + metronidazole[89]
Pyelonephritis	2nd and 3rd trimester more commonly than 1st trimester	Urinalysis, urine culture; obtain imaging to evaluate for renal abscess if patient is clinically toxic or hemodynamically unstable[70,71,73]	Immunocompetent: ceftriaxone, cefepime, ampicillin + gentamicin Immunocompromised: piperacillin/tazobactam, carbapenem[73,75,76,106]
Pneumonia	1st, 2nd, and 3rd trimester	Chest radiograph, consider ultrasound[46,58–60]	Pneumococcal beta-lactam + macrolide MRSA coverage if suspected: vancomycin, linezolid[12,62]
Endometritis	Post-partum	Computed tomography[105]	IV gentamicin + clindamycin, doxycycline + cefoxitin, ampicillin/sulbactam[100,101]

MRSA, methicillin-resistant *Staphylococcus aureus*; *IV,* intravenous.

with positive blood cultures had a level of 2.2 mmol/L.[108] This study found increased morbidity with elevated lactic acid, with an adjusted odds ratio of 2.34 per 1 mmol/L increase in lactic acid.[108]

No specific guidelines exist for vasopressors preference in pregnant patients. Although there is no explicit recommendation for mean arterial pressure optimization for sepsis in pregnancy, 65 mm Hg is a reasonable resuscitation goal.[107] Fetal monitoring can provide further titration feedback.[109] The 2016 Society of Critical Care Medicine guidelines do not offer recommendations tailored for the pregnant patient, although their current data support the use of norepinephrine as the first-line vasopressor in pregnant septic patients.[77,107,110] Due to the paucity of data, there is scant evidence to suggest that administration of norepinephrine causes negative fetal outcomes, or to suggest how norepinephrine administration impacts fetal outcome.[111]

The choice for second-line vasopressor has been extrapolated from controlled studies with spinal anesthetics and is therefore controversial for application in sepsis.[112-116] Phenylephrine and ephedrine are often used as second-line agents, although with known tachyphylaxis.[1107,114,116] Unlike ephedrine, phenylephrine does not alter the fetal acid-base status, although its alpha stimulation generates reflex maternal bradycardia and diminished cardiac output.[114,115] In comparison, ephedrine does not generate bradycardia, although its indirect action to release pre-existing maternal catecholamines may prove less efficacious in a septic patient who has already exhausted her endogenous stores and expended her cardiac reserve.[113-115]

The data on vasopressor use in pregnancy are typically derived from C-section deliveries, many of which are elective.[65,113,114] In the Task Force on Obstetric Anesthesia, the American Society of Anesthesiologists recommended phenylephrine over ephedrine because of the preferred fetal acid-base status, as ephedrine causes fetal acidemia.[112] While this choice was supported by an international consensus of counterpart agencies, these data are extrapolated from a different physiologic context.[117]

In the rare setting of septic myocarditis, dobutamine is the preferred inotrope.[113] Despite its very limited use in the non-pregnant septic population, dobutamine presents a viable option to improve inotropy in pregnant patients already on vasopressors and fluids.[112,118] Based on previous ovine models, dobutamine provides inotropy in pregnant sheep, although it decreases uterine blood flow; it requires further study in humans.[119]

Other treatment considerations in maternal sepsis include glucose control, steroids, and venous thromboembolism (VTE) prophylaxis. Maternal hyperglycemia can directly cause fetal hyperglycemia and ultimately acidosis, decreasing uterine blood flow and lowering fetal oxygenation.[109] Maternal blood glucose should be maintained less than 180 grams per deciliter.[109] Steroids are recommended by the American College of Obstetrics and Gynecology in women between 24 weeks and 33 weeks and six days who are at risk of a preterm delivery within seven days, which is inclusive of those with rupture of membranes.[120] Hydrocortisone should be considered in those patients who do not improve with IV fluids and vasopressors.[107,110] Pregnancy alone confers a five-fold increased risk of deep vein thrombosis as compared to the non-pregnant population.[122] In individuals in septic shock on VTE prophylaxis, there was a 37% incidence in VTEs despite these prophylactic interventions. As septic pregnant patients are at high risk of VTE, patients without contraindications should receive both intermittent compression devices and either daily LMWH or 2-3 times daily administration of unfractionated heparin.[109,122] Direct oral anticoagulants are not currently recommended.[109]

CONCLUSION

The anatomic and physiologic changes of pregnancy pose a challenge in early recognition and management of sepsis. Current sepsis guidelines were extrapolated from randomized control trials that specifically excluded pregnant patients. Although new guidelines have been created to risk stratify pregnant patients, they are without significant validation. Further research and validation are needed to help properly recognize and treat this small but critically ill population to improve outcomes for both mother and fetus.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.The views expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, the Department of Defense, or the U.S. government.

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Incidence and Causes of Iatrogenic Hypoglycemia in the Emergency Department

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Section Editor: Michael Abraham, MD
Submission history: Submitted March 6, 2019; Accepted July 14, 2019
Electronically published [date]
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.42996

Introduction: Hypoglycemia is frequently encountered in the emergency department (ED) and has potential for serious morbidity. The incidence and causes of iatrogenic hypoglycemia are not known. We aim to describe how often the cause of ED hypoglycemia is iatrogenic and to identify its specific causes.

Methods: We included adult patients with a chief complaint or ED diagnosis of hypoglycemia, or an ED glucose value of ≤70 milligrams per deciliter (mg/dL) between 2009–2014. Two independent abstractors each reviewed charts of patients with an initial glucose ≤ 50 mg/dL, or initial glucose ≥ 70 mg/dL with a subsequent glucose ≤ 50 mg/dL, to determine if the hypoglycemia was caused by iatrogenesis. The data analysis was descriptive.

Results: We reviewed the charts of 591 patients meeting inclusion criteria. Of these 591 patients, 99 (17%; 95% confidence interval, 14-20%) were classified as iatrogenic. Of these 99 patients, 61 (61%) cases of hypoglycemia were caused by insulin administration and 38 (38%) were caused by unrecognized malnutrition. Of the 61 patients with iatrogenic hypoglycemia after ED insulin administration, 45 and 15 patients received insulin for hyperkalemia and uncomplicated hyperglycemia, respectively. One patient received insulin for diabetic ketoacidosis.

Conclusion: In ED patients with hypoglycemia, iatrogenic causes are relatively common. The most frequent cause was insulin administration for hyperkalemia and uncomplicated hyperglycemia. Additionally, patients at risk of hypoglycemia in the absence of insulin, including those with alcohol intoxication or poor nutritional status, should be monitored closely in the ED. [West J Emerg Med. 2019;20(5)833-837.]

INTRODUCTION

Hypoglycemia is a serious and common condition that can cause seizures, loss of consciousness, and death. Emergency departments (EDs) often treat this pathology.[1] A longitudinal study demonstrated that EDs treat more than 95,000 patients for hypoglycemia annually, comprising 3.4% of the entire diabetic population, of which 25% required hospital admission.[1,2] While hypoglycemia is commonly caused by factors such as missing meals, wrong insulin medication or dose at home, hypoglycemia can also be caused by iatrogenesis.[1,3]

Iatrogenic hypoglycemia places the patient at risk of serious harm. This topic has been studied in hospitalized patients, but ED literature is limited.[1,3] Iatrogenic hypoglycemia is often avoidable, and medical errors are common. In a voluntary survey of physician errors 76% of mistakes occurred during the initial testing and clinical assessment of the patient.[4] ED patients may be at higher risk for hypoglycemia than the general population, especially those who receive insulin in the ED (for hyperkalemia or hyperglycemia, among other indications) and those who are acutely or chronically malnourished. Understanding the causes of iatrogenic hypoglycemia may assist emergency physicians in preventing this complication from occurring. In this study, we sought to determine the frequency and causes of iatrogenic hypoglycemia in an urban ED.

Population Health Research Capsule

What do we already know about this issue?
Iatrogenic hypoglycemia frequently occurs in the ED and may cause serious morbidity and mortality.

What was the research question?
How often does iatrogenic hypoglycemia occur in the ED and what are its causes?

What was the major finding of the study?
Patients receiving insulin for hyperglycemia or hyperkalemia or who have alcohol intoxication are at increased risk.

How does this improve population health?
Being aware of these high-risk populations may help ED physicians prevent future cases of iatrogenic hyperglycemia.

METHODS

Study Design and Setting

This was a retrospective, observational study conducted in the ED of an urban level 1 trauma center that cares for approximately 100,000 patients annually. The institutional review board approved this study.

Selection of Participants

A data analyst identified adult (>18 years old) ED patients with hypoglycemia between 2009-2014 in the electronic health record (EHR) by searching for patients with an ED chief complaint or discharge diagnosis of hypoglycemia, or any ED glucose value ≤70 milligrams per deciliter (mg/dL) (local laboratory cutoff). In seeking to identify potential iatrogenic causes of hypoglycemia, we performed structured reviews of charts of patients with one or more initial ED glucose values of ≤50 mg/dL, and those with an initial glucose ≥70 mg/dL with one or more subsequent glucose values ≤50 mg/dL. We chose a cutoff of 50 mg/dL rather than a laboratory cutoff of 70 md/dL because glucose values ≤50 mg/dL have greater clinical significance and are more likely to be associated with patient harm; we selected a decrement from ≥70 mg/dL to ≤50 mg/dL because decrements of less than 20 mg/dL were less likely to be due to iatrogenic causes.

Methods of Measurement

Patient demographics, chief complaint, ED diagnosis, and glucose values were abstracted from the EHR (Epic Systems, Verona, WI). Two trained abstractors independently performed a structured chart review for each identified patient.[5] To determine whether the hypoglycemia was iatrogenic, the abstractors reviewed nursing and physician notes, laboratory results, vital signs, ED orders, and medications administered during the ED encounter. Iatrogenic hypoglycemia was defined as hypoglycemia (glucose ≤50 mg/dL) that occurred in the ED caused by 1) ED insulin administration, or 2) unrecognized or inadequately treated malnutrition. There are other causes of hypoglycemia (eg, sulfonylurea overdose, liver disease, and sepsis), but for the purposes of this study we only examined for the two most common causes of iatrogenic hypoglycemia.

Malnutrition was defined as any of the following: poor or reduced oral intake documented in the physician's note; acute alcohol intoxication; chronic alcohol dependence; or inability to eat or drink in the ED (eg, an agitated patient who was sedated and placed in restraints, or patients with a nil per os diet order). We recorded the indication for insulin use if hypoglycemia was related to ED insulin administration. If the two reviewers disagreed whether the hypoglycemia was iatrogenic, a third abstractor reviewed the chart to make a final determination. To estimate interobserver agreement, we calculated an unadjusted kappa value for the initial two reviewers.

Data Analysis

All data analyses are descriptive. Baseline characteristics are described using medians or proportions as appropriate. The proportion of ED visits with hypoglycemia deemed iatrogenic was reported, along with 95% confidence intervals (CI) and etiologies of iatrogenic hypoglycemia. Because there is no prior ED data, no a priori sample size was calculated. We used Stata (Version 12, Stata Corporation, College Station, TX) for all data analyses.

RESULTS

Between 2009–2014, there were 2,858 patients who met initial inclusion criteria based on the chief complaint or ED diagnosis of hypoglycemia, or an ED glucose value ≤70 mg/dL.

Of these 2,858 patients, we reviewed the charts of 591 (21%) who had an initial glucose ≤50 mg/dL or a decrement in glucose from ≥70 mg/dL to ≤50 mg/dL to determine if the hypoglycemia was iatrogenic. Baseline characteristics are presented in Table 1. Of these 591, 99 (17%; 95% CI, 14-20%) patients were determined to have iatrogenic hypoglycemia (Table 2). Interobserver agreement for iatrogenic hypoglycemia was 90% (kappa 0.63); disagreements were resolved by a third physician. The final rate reported reflects the outcomes of the adjudicated cases by the third reviewer.

The most frequent cause of iatrogenic hypoglycemia was insulin administration, for both uncomplicated hyperglycemia and for hyperkalemia. Details on the causes of iatrogenic hypoglycemia are presented in Table 2. Of those with iatrogenic hypoglycemia 40 patients (40%) had diabetes, while 59 (60%) did not.

DISCUSSION

This study demonstrates that hypoglycemia in ED patients is commonly caused by iatrogenesis. In particular, insulin administration for hyperkalemia and uncomplicated hyperglycemia were frequent culprits. Unrecognized malnutrition in our population, especially in the context of alcohol intoxication, was another important cause of hypoglycemia that could have been prevented by more careful care.

Prior literature supports insulin administration as an important cause of iatrogenic hypoglycemia.[6,7] Hyperkalemia is most prevalent in patients with end stage renal disease on chronic dialysis, and insulin is often administered in the ED to patients with hyperkalemia to shift potassium to the intracellular space until dialysis is available.[4,7,8] Renal insufficiency leads to decreased insulin clearance, which increases the risk of hypoglycemia.[9] A recent study demonstrated that 17% of ED patients who receive insulin for hyperkalemia develop hypoglycemia within three hours.[10] The risk of hypoglycemia may be mitigated by administering smaller doses of insulin, larger doses of dextrose, or by more careful monitoring after insulin administration.[10] With close monitoring even massive doses of insulin can be administered safely, as they are used to treat calcium-channel blocker and beta-blocker poisoning.[11] Additionally, iatrogenic hypoglycemia is known to occur after ED insulin therapy for uncomplicated hyperglycemia; ED glucose reduction for uncomplicated hyperglycemia may lack value and consumes time and resources.[12,13]

Malnutrition, caused by alcohol intoxication or dependence, or reduced oral intake, was also found to be a common cause of iatrogenic hypoglycemia. Patients who present with chronic alcohol dependence or acute alcohol intoxication are likely to have depleted glycogen stores with concomitant gluconeogenesis inhibition secondary to poor nutrition and relative thiamine

Table 1. Baseline characteristics of patients with hypoglycemia.

Characteristic	All patients (N=591)	Patients with iatrogenic hypoglycemia (N=99)
Age, median (IQR) - years	51 (39-62)	49 (34-58)
Male gender - number (%)	346 (59)	63 (64)
Chief complaint - number (%)*		
Low blood sugar	134 (23)	0
Altered mental status	84 (15)	25 (25)
Abdominal pain	33 (6)	11 (11)
Chest pain	28 (5)	2 (2)
Shortness of breath	24 (4)	6 (6)
Fall	15 (3)	2 (2)
Dizziness	11 (2)	0
Weakness	11 (2)	3 (3)
Vomiting	10 (2)	1 (1)
High blood sugar	8 (1)	6 (6)
First recorded glucose, median (IQR) -mg/dL	48 (40-95)	97 (77-148)
Lowest recorded glucose, median (IQR) - mg/dL	41 (33-46)	42 (32-47)
Highest recorded glucose, median (IQR) - mg/dL	163 (116-238)	177 (121-237)

This table displays baseline characteristics for all patients meeting our initial inclusion criteria for hypoglycemia as well as patients deemed to have iatrogenic hypoglycemia.
*Only the 10 most common chief complaints are displayed in this table. Altered mental status is commonly used in our ED when a patient presents with alcohol intoxication.
IQR, interquartile range; *mg/dL,* milligrams per deciliter

Table 2. Study outcomes and emergency department management of hypoglycemia.

Parameter	Value (n=591)
Iatrogenic hypoglycemia number (%; 95% CI)	99 (17; 14-20)
Cause of iatrogenic hypoglycemia number (%)	
Insulin administered	61/99 (61)
Uncomplicated hyperglycemia	15/61 (25)
Diabetic ketoacidosis	1/61 (2)
Hyperkalemia	45/61 (74)
Malnutrition not recognized	38/99 (31)
Alcohol intoxication or dependence	29/38 (76)
Inability to eat in the ED	9/38 (24)
Parenteral ED management of hypoglycemia number (%)	
Dextrose containing fluids, 5% or 10%	54 (9)
Dextrose 50%	351 (59)
Glucagon	3 (1)

ED, emergency department; *CI,* confidence interval.

deficiency, and consequently are at higher risk for hypoglycemia.[14] This patient population has many comorbidities; caring for acute intoxication and concomitant illnesses may distract from routine glucose monitoring, which is especially important when oral intake is limited by intoxication or parenteral sedation.[15] Hypoglycemia in this patient population was recently found to be an independent predictor of subsequent critical illness.[16] Additionally, these data support more careful monitoring of non-intoxicated patients who are placed nil per os.

We did not measure more patient-centered outcomes such as cost, hospital length of stay, encephalopathy from hypoglycemia, or mortality. However, preventing hypoglycemia is important for patient-safety, and hypoglycemia has been associated with poor outcomes.[17-19] These data demonstrate and remind emergency physicians that care must be taken when administering insulin or caring for patients at risk of malnutrition.

LIMITATIONS

We decided to search for only those with significant iatrogenic hypoglycemia (ie, those with nadir glucose ≤50 mg/dL who started at 70 mg/dL or higher), which may underestimate the true incidence of iatrogenic hypoglycemia. Additionally, malnutrition, though defined a priori, could have been interpreted subjectively due to potentially incomplete medical records and variations among abstractors. We attempted to mitigate this by having two abstractors review each patient chart. These limitations emphasize that the estimated value for iatrogenic hypoglycemia should not be viewed as a precise rate. Rather, it highlights the relatively common nature of this problem in the ED.

We care for a large socioeconomically disadvantaged population with a high burden of chronic disease, alcohol and drug dependence, and homelessness. These results may not generalize to other institutions that care for different patient populations. Our limited study population (n=99) also restrains the generalizability of these results. A larger multicenter study would provide greater external validity.

CONCLUSION

In this retrospective study of hypoglycemia in the ED, patients without diabetes developed iatrogenic hypoglycemia more commonly than patients with diabetes. Insulin administration, especially in the context of hyperkalemia and uncomplicated hyperglycemia, was the most common cause of iatrogenic hypoglycemia. Additionally, patients at risk of hypoglycemia in the absence of insulin, including those with acute alcohol intoxication or poor nutritional status, must be vigilantly monitored while in the ED.

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Conflicts of Interest: By the *West*JEM article submission agreement, all authors are required to disclose all affiliations, funding sources and financial or management relationships that could be perceived as potential sources of bias. No author has professional or financial relationships with any companies that are relevant to this study. There are no conflicts of interest or sources of funding to declare.

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This Article Corrects: "Development of a Clinical Teaching Evaluation and Feedback Tool for Emergency Medicine Faculty"

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Electronically published August 20, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.7.44616

West J Emerg Med. 2019 January;20(1):50-57
Development of a Clinical Teaching Evaluation and Feedback Tool for Emergency Medicine Faculty
Dehon E, Robertson E, Barnard M, Gunalda J, Puskarich M

Erratum in
West J Emerg Med. 2019 September;20(5):838-839. There was an error on Figure 1. Faculty Shift Card. The top card originally stated, "What should this faculty member do to improve their procedural teaching skills? Select all that apply." This should be revised to, "What should this faculty member do to improve their clinical decision making teaching skills? Select all that apply" with the following recommendations: Engage in more collaboration with resident about clinical decisions; Ask more leading questions prior to clinical decisions; Direct resident to helpful resources; Maximize teaching opportunities; Nothing.

Abstract
Introduction: Formative evaluations of clinical teaching for emergency medicine (EM) faculty are limited. The goal of this study was to develop a behaviorally-based tool for evaluating and providing feedback to EM faculty based on their clinical teaching skills during a shift.

Methods: We used a three-phase structured development process. Phase 1 used the nominal group technique with a group of faculty first and then with residents to generate potential evaluation items. Phase 2 included separate focus groups and used a modified Delphi technique with faculty and residents, as well as a group of experts to evaluate the items generated in Phase 1. Following this, residents classified the items into novice, intermediate, and advanced educator skills. Once items were determined for inclusion and subsequently ranked they were built into the tool by the investigators (Phase 3).

Results: The final instrument, the "Faculty Shift Card," is a behaviorally-anchored evaluation and feedback tool used to facilitate feedback to EM faculty about their teaching skills during a shift. The tool has four domains: teaching clinical decision-making; teaching interpersonal skills; teaching procedural skills; and general teaching strategies. Each domain contains novice, intermediate, and advanced sections with 2-5 concrete examples for each level of performance.

Conclusion: This structured process resulted in a well-grounded and systematically developed evaluation tool for EM faculty that can provide real-time actionable feedback to faculty and support improved clinical teaching.

PMCID: PMC6324693 [PubMed - indexed for MEDLINE]

During this shift, how well did the selected attending facilitate the development of your clinical decision making skills?				
Novice	□	Intermediate	□	Expert
Ensures that the resident structures the patient presentation appropriately Rarely includes the resident in clinical decision-making Allows resident complete autonomy and rarely participates in clinical decision-making		Models clinical decision-making skills and explains decision-making process Elicits the resident's diagnosis and plan and avoids giving the answer Engages in collaborative decision-aking with the resident Has the resident provide rationale for decision (not allowing a shotgun approach) Facilitates responses from the resident through leading questions or provision of choices		Uses illness scripts and data from the literature Changes a scenario to maximize teaching opportunities or discuss unusual diagnoses Points out multiple ways to work up or treat a patient Encourages evidence-based medicine dialogue on cognitive errors Directs resident to helpful resources, especially algorithms, decision rules, treatment protocols
What should this faculty member do to improve their clinical decision making teaching skills? Select all that apply. □ Engage in more collaboration with resident about clinical decisions □ Ask more leading questions prior to clinical decisions □ Direct resident to helpful resources □ Maximize teaching opportunities □ Nothing Comments:				
During this shift, how well did the selected attending facilitate the development of your procedural skills?				
Novice	□	Intermediate	□	Expert
Performs procedure without resident participation Rarely or never observes resident while they perform procedures		Determines/assesses level of trainee knowledge before procedure Coaches in real time with a calm demeanor Debriefs after procedure and provides feedback Reiterates key steps		Ensures that preparation and patient positioning is done correctly Points out real-time tricks Allows resident to respond to difficult situations; provides guidance but does not take over (assuming it's safe for the patient)
What should this faculty member do to improve their procedural teaching skills? Select all that apply. □ Coach in real time □ Provide feedback in timely fashion after procedure □ Reiterate key steps, preparation, patient positioning □ Allow resident to respond in difficult situations □ Nothing □ N/A-no procedures done this shift Comments:				

Figure 1. Faculty shift card 1.

This Article Corrects: "Burnout, Drop Out, Suicide: Physician Loss in Emergency Medicine, Part 1"

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Electronically published August 21, 2019
Full text available through open access at http://escholarship.org/uc/uciem_westjem
DOI: 10.5811/westjem.2019.8.44927

West J Emerg Med. 2019 January;20(3):485-494
Burnout, Drop Out, Suicide: Physician Loss in Emergency Medicine, Part 1
Stehman CR, Testo Z, Gershaw RS, Kellogg AR

Erratum in
West J Emerg Med. 2019 November;20(6):840-841. The authors would like to revise the description on the evolution of the definition of burnout in the Introduction. The introduction formerly stated, "Based on his research, Freudenberger used "burnout" as shorthand for a psychological syndrome with three dimensions: emotional exhaustion, depersonalization, and reduced personal accomplishment.[2] Maslach subsequently summarized the dimensions of burnout as "exhaustion," "cynicism," and "inefficacy," providing more identifiable definitions of each dimension that align well with her measurement tool.[3]"

This should be revised to the following: "Based on his experiences, Freudenberger described the phenomenon of "burn-out", subsequently defined by Maslach as a psychological syndrome with three dimensions: emotional exhaustion, depersonalization, and reduced personal accomplishment.[2,3]"

Abstract
Each year more than 400 physicians take their lives, likely related to increasing depression and burnout. Burnout—a psychological syndrome featuring emotional exhaustion, depersonalization, and a reduced sense of personal accomplishment—is a disturbingly and increasingly prevalent phenomenon in healthcare, and emergency medicine (EM) in particular. As self-care based solutions have proven unsuccessful, more system-based causes, beyond the control of the individual physicians, have been identified. Such system-based causes include limitations of the electronic health record, long work hours and substantial educational debt, all in a culture of "no mistakes allowed." Blame and isolation in the face of medical errors and poor outcomes may lead to physician emotional injury, the so-called "second victim" syndrome, which is both a contributor to and consequence of burnout. In addition, emergency physicians (EP) are also particularly affected by the intensity of clinical practice, the higher risk of litigation, and the chronic fatigue of circadian rhythm disruption. Burnout has widespread consequences, including poor quality of care, increased medical errors, patient and provider dissatisfaction, and attrition from medical practice, exacerbating the shortage and maldistribution of EPs. Burned-out physicians are unlikely to seek professional treatment and may attempt to deal with substance abuse, depression and suicidal thoughts alone. This paper reviews the scope of burnout, contributors, and consequences both for medicine in general and for EM in particular.

PMCID: PMC6526882 [PubMed - indexed for MEDLINE]

INTRODUCTION

"Burnout" evokes images of harried, sleep-deprived, hungry physicians, overwhelmed with "paperwork," administrative complaints of missed metrics, and pending tasks for family and patients. For the physician suffering from burnout, recovery can seem daunting or even impossible. For healthcare, burnout has been branded an epidemic, with societal and human economic and personal costs.[1] This article, the first of two parts, synthesizes information on burnout—the scope of the problem, its causes and consequences—from the perspective of the emergency physician (EP). Part II will focus on wellness and seek to make recovery less daunting.

Burnout: Definition and Measurement

Burnout is a complex condition with a history in many disciplines. Based on his experiences, Freudenberger described the phenomenon of "burn-out", subsequently defined by Maslach as a psychological syndrome with three dimensions: emotional exhaustion, depersonalization, and reduced personal accomplishment.[2,3] Those who score high in "exhaustion" feel over-extended, their emotional and physical resources depleted.[3] High scorers in "cynicism" (depersonalization) appear more callous or detached than would be expected for normal "coping."[3] Those lacking confidence or feeling they have achieved little work success score high in the "inefficacy" (reduced personal accomplishment) dimension.[3] Overall, sufferers from burnout are frequently exhausted, diminished in their ability to care, and feel as though their work makes little difference.

Maslach used these definitions to create the most frequently used assessment tool for identifying burnout, the Maslach Burnout Inventory (MBI). This tool contains 22 questions addressing the three dimensions and provides scores in each. The higher the score, the higher the burnout in that dimension.[4] Rather than a dichotomous cutoff score of burnout as a diagnosis, the MBI describes a spectrum with higher scores equating to more severe symptoms and consequences.[5] While the MBI has been modified and abbreviated for specific populations and ease of use, it remains proprietary. The next most common tool used in healthcare burnout research, the Oldenburg Burnout Inventory, focuses on emotional exhaustion and depersonalization/ disengagement, while leaving out personal accomplishment.[6] A list of burnout assessment tools appears in Appendix 1; however, readers may consider simply asking physicians if they are burned out: In one study, self-reported burnout accurately predicted meeting MBI burnout criteria 72% of the time.[7]

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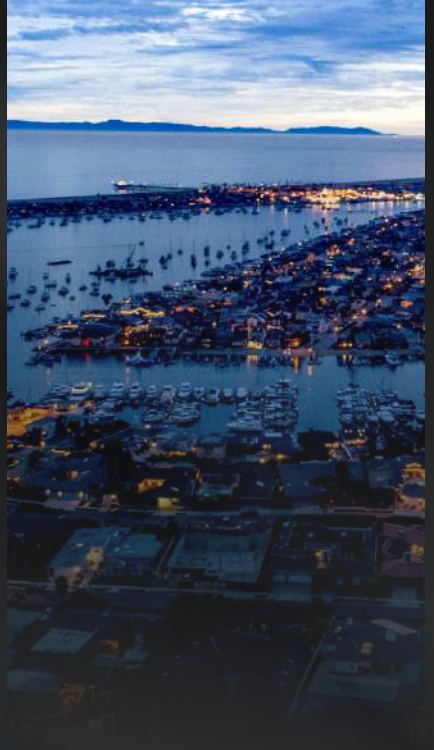
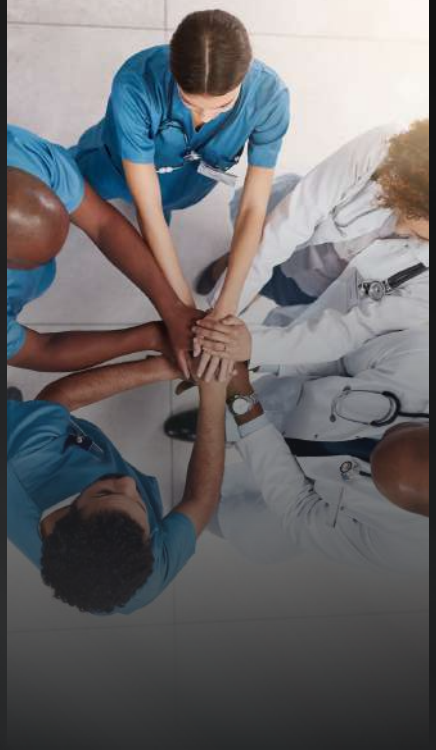
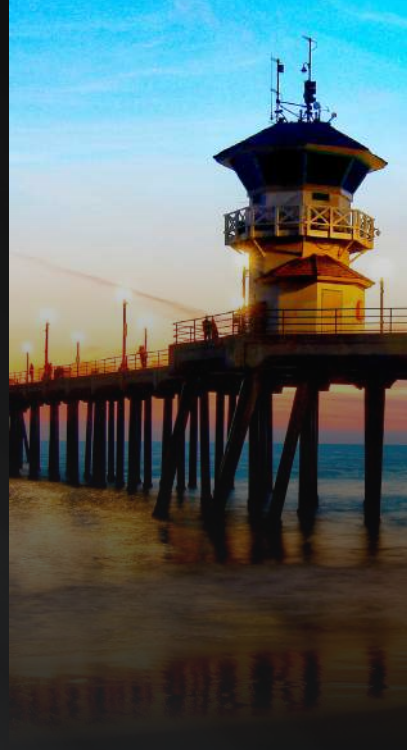

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