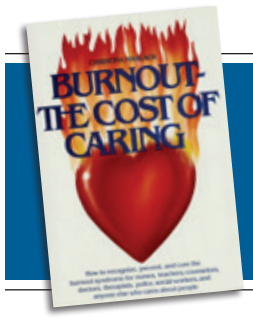

DR. MASLACH Q&A

The Roots of Burnout

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PHARM 360

"A Bat Flew Into My Head"

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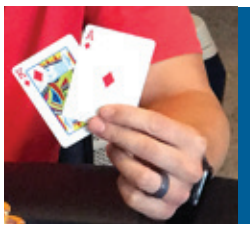

THE FEED

EM Doc Hold 'Em

SEE PAGE 43

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LAWSUIT

DEFENDING "PRUDENT LAYPERSON" IN COURT

SEE PAGE 6

2019 CODING UPDATE

DISSECTING THE 2019 PROPOSED RULE

SEE PAGE 21

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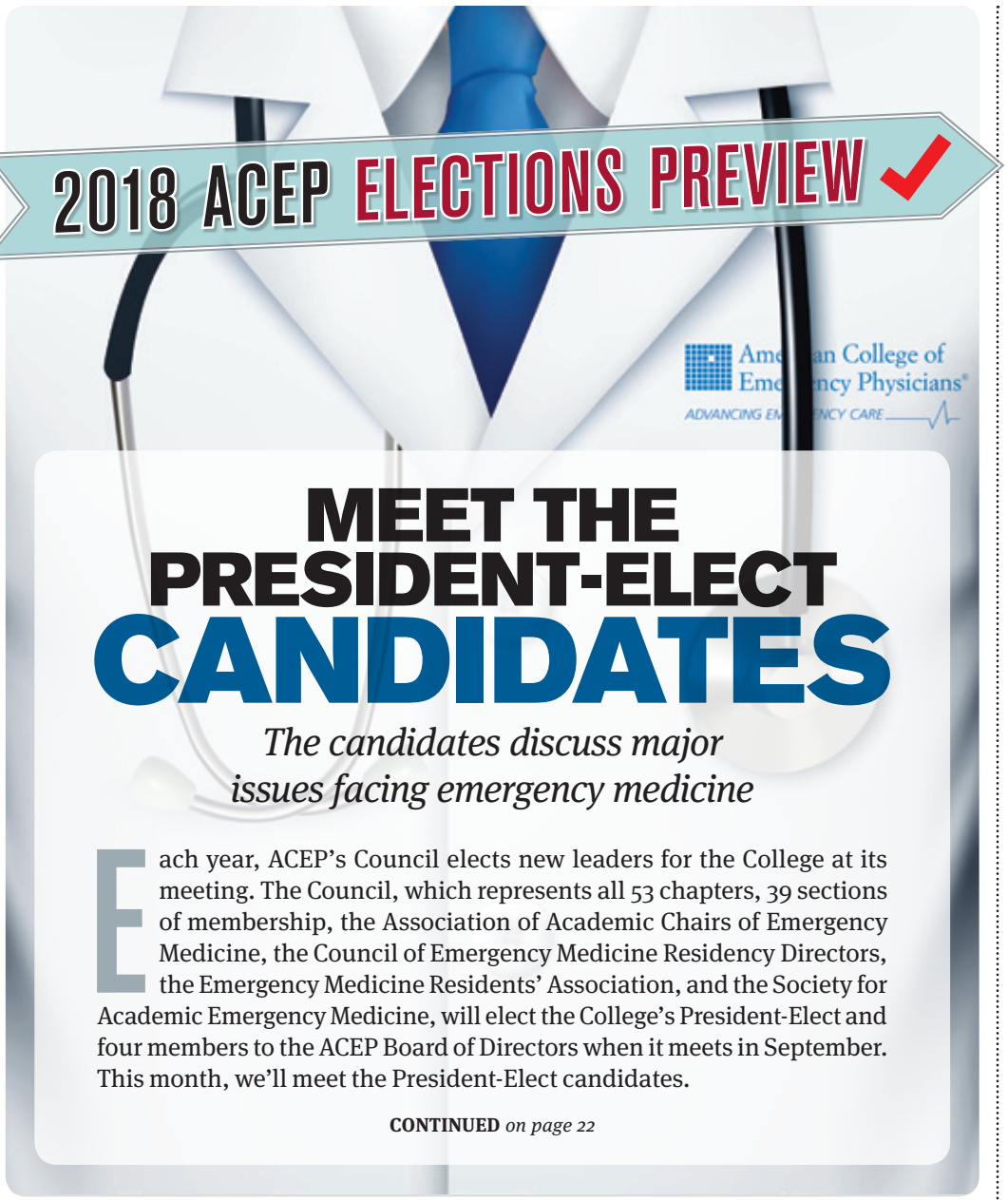

MEET THE PRESIDENT-ELECT CANDIDATES

The candidates discuss major issues facing emergency medicine

Each year, ACEP's Council elects new leaders for the College at its meeting. The Council, which represents all 53 chapters, 39 sections of membership, the Association of Academic Chairs of Emergency Medicine, the Council of Emergency Medicine Residency Directors, the Emergency Medicine Residents' Association, and the Society for Academic Emergency Medicine, will elect the College's President-Elect and four members to the ACEP Board of Directors when it meets in September. This month, we'll meet the President-Elect candidates.

CONTINUED *on page 22*

TIRELESS DEFENSE OF EM

Dr. Greg Henry waxes eloquently on ACEP's history—and future

As part of our celebration of ACEP's 50th anniversary, *ACEP Now* Medical Editor-in-Chief Kevin Klauer, DO, EJD, FACEP, recently sat down with ACEP Past President Gregory L. Henry, MD, FACEP, clinical professor in the department of emergency medicine at the University of Michigan Medical School in Ann Arbor, to discuss key moments in ACEP's history and to consider what might be in store for ACEP's future. Here are some highlights from their conversation.

KK: I'm so excited to culminate the 50th anniversary series with, you, Dr. Henry. You always have words of wisdom in many circumstances. Over the course of your time with ACEP, what are some notable points in history regarding the specialty?

GH: I remember those days [becoming a specialty] clearly because I was living in the Phi Rho Sigma medical fraternity house across the street from St. Joseph Mercy Hospital [in Ann Arbor]. One day in 1968, I went to the ED. The gentleman who would usually let me shadow him [George Fink, MD] was gone.

George had gone to Lansing to sign the papers for a new organization called ACEP. Things had changed in America since the end of the Second World War. There was huge mobility, and lots of people didn't have doctors. We also learned that we needed to be proactive to change the outcome of certain diseases. Shakespeare said it best: "Diseases desperate grown by desperate appliance are relieved, or not at all." The emergency departments in the United States had been staffed by fill-in people who were dermatologists, allergists, internal medicine,

CONTINUED *on page 10*

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2018–2019 COMPENSATION REPORT FOR EMERGENCY PHYSICIANS

PAGE 19

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1. Dunne RB and Shortt S. Comparison of bronchodilator administration with vibrating mesh nebulizer and standard jet nebulizer in the emergency department. The American journal of emergency medicine. 2017

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NEWS FROM THE COLLEGE

UPDATES AND ALERTS FROM ACEP

ACEP President Responds to *New York Times* Article on Medical Liability Limits

"Hospital emergency departments are unique in that they have a federal mandate to screen and stabilize everyone who comes through the door, regardless of ability to pay. We also care for the most severely ill and injured patients who are at greatest risk of dying. Liability protections need to be in place for physicians who provide federally mandated emergency services. It would not only save a lot of money, but it would also help ensure that emergency physicians and the on-call medical specialists that are needed will be there." Read the full letter from ACEP President Paul Kivela, MD, MBA, FACEP, at ACEP.org.

ACEP-led Provision Boosts Prescription Drug Monitoring Programs

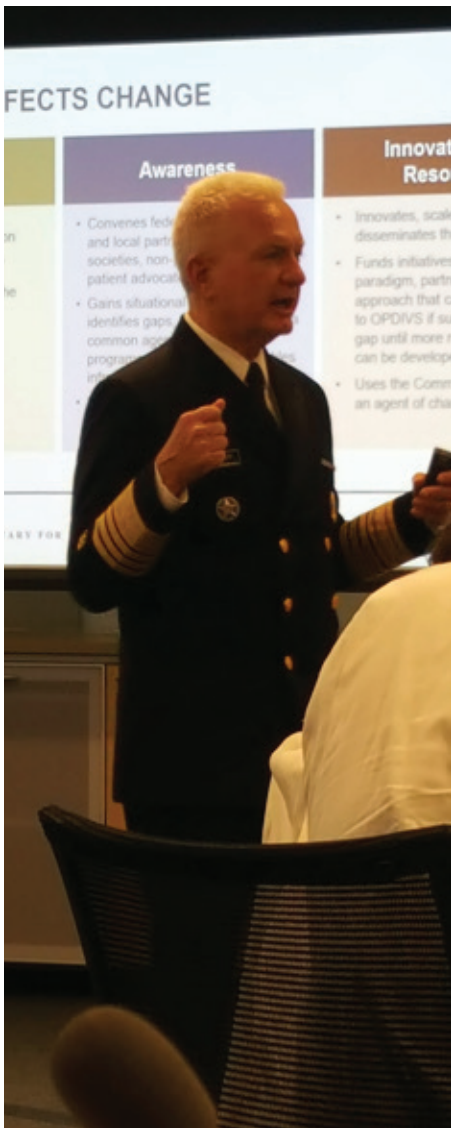
An ACEP-developed provision that requires the Department of Defense to share controlled substance prescribing information of TRICARE beneficiaries with state prescription drug monitoring programs was successfully passed into law as part of H.R. 5515, the John S. McCain National Defense Authorization Act for Fiscal Year 2019. ACEP staff worked closely with Rep. Mike Turner (D-OH) to develop this legislative effort and ensure its inclusion in this year's defense authorization bill.

ACEP Teams Up to Improve ED Sickle Cell Disease Care ▶

The Emergency Department Sickle Cell Care Coalition (EDSC3) hosted a one-day leadership summit on Aug. 16, 2018, at the American Society of Hematology's headquarters in Washington, D.C. The purpose of this summit was to identify concrete and specific actions to improve care in the emergency department for children and adults living with sickle cell disease (SCD). A variety of leaders from key organizations discussed current initiatives and how to collaborate to effectively and efficiently disseminate best practices to improve the emergency department care for children and adults with SCD. The keynote address was presented by Adm. Brett P. Giroir, MD, assistant secretary for health at the U.S. Department of Health and Human Services.

Continuing ACEP Advocacy for Physicians and Patients

- ACEP was invited by AHIP, a trade association for commercial insurers, to participate in a meeting of payers seeking input on expanding use of non-opioid pain management. Other physician groups invited to participate were the American Medical Association (AMA), American College of Physicians, and American Academy of Family Physicians.
- ACEP contributed information to, and coordinated with, Sen. Claire McCaskill (D-MO) on her report detailing Anthem's retroactive denials of emergency care coverage that was released late last month. (See page 6 for more on ACEP's efforts to combat retroactive denials of emergency department visits.)
- ACEP participated by invitation in a convening by the White House's Office of National Drug Control Policy on efforts to address the opioid epidemic.
- ACEP participated by invitation in a roundtable discussion on health care price transparency initiated by Senators Bill Cassidy (R-LA), Michael Bennet (D-CO), Chuck Grassley (R-IA), Tom Carper (D-DE), Todd Young (R-IN), and Claire McCaskill (D-MO). ACEP was one of only three physician associations in attendance, joining the AMA and the American College of Surgeons. Among the other groups participating were the American Hospital Association, insurers and brokers, and patient advocates.
- ACEP was the only medical association invited to participate in a meeting on price transparency at the Department of Health and Human Services. Demetrios Kouzoukas, principal deputy administrator of the Centers for Medicare and Medicaid Services (CMS) and director of the Center for Medicare, attended the majority of the session.
- ACEP attended multiple listening sessions with CMS to discuss proposals related to the 2019 Physician Fee Schedule and Quality Payment Program Proposed Rule. ⊕



ACEP

Adm. Brett P. Giroir, MD, delivers the keynote address at the Emergency Department Sickle Cell Care Coalition summit.

SEND YOUR THOUGHTS AND COMMENTS TO ACEPNOW@ACEP.ORG

THE BREAK ROOM

More Retirement Advice

I thought your "Retirement Tips" article [June 2018] fell short of giving tested, practical advice to the many ACEP members facing retirement questions. It did so precisely because it solicited input from well-known, august, and wonderful over-achieving emergency physicians. It lacked tips from a single, simple, everyday emergency physician who had not achieved national business or leadership success.

My tips would have been quite different. I did full-time clinical medicine for 40 years. Yes, I had volunteer stints in ACEP leadership, but no business or practice leadership. And I've been retired for two years now, for real, unlike any of the honored leaders you quoted. Here's what I would have said:

Plan to retire before they ask you to retire. Night shifts are impossible in your sixties. Your body starts slowing down in your fifties and you'll have noticeable and significant physical slowing in your sixties, making it harder to keep up the pace of a busy ED shift. Your mental endurance will also decrease. See if you like urgent care or clinics, but realize that that is not emergency medicine (I didn't like them: busy and boring).

Pick a date and stick to it. Prepare yourself for the realization that you will never be a practicing doctor again, but that you will be starting a different life of your choice. Make sure the mortgage is paid off (my biggest mistake) and the kids are on their way in life. Keep your medical license for a year to be sure you don't have regrets and want to go back to practice. If you don't resume practice, most of us will not be able to afford the cost of maintaining a license and DEA registration and CME; surrender your license and be proud of your MD, your FACEP, and your past career.

Focus on your new career. ED docs have many interests; pick some and make a new career. I chose medical school admissions committee and lilac horticulture as my main hobbies; they are just as fulfilling although a bit lonelier, especially since, like in a divorce, many people you cared about fall out of your life. But others will arise to take their place.

Now that you have more time for family, don't expect them to have time for you. They are busy with their lives and careers. Your spouse, however, can be a wonderful source of companionship and comfort. And grandchildren are so much more interesting and fun than children.

Money is less available, and you have to learn to make healthier financial decisions. Realize this is a new life path, and expensive dinners at the best restaurants are now to be rare treats. That's life. The biggest problem is getting your still-working friends to realize you no longer have the money to spend like they do.

Travel options open up. I hope you had separate savings for the extensive travel you can do. Travel early and often while your health is good, and inflation hasn't eaten away your savings. Remember that lying on a beach and reading, while still fun, is no longer necessary to recuperate.

And lastly, don't count on continued good health. Years of racquetball or tennis or running will show up with damaged and arthritic knees and hips, which will limit your physical abilities and endurance. Plan for it and don't be discouraged. Do as much as you can.

Retirement can be a wonderful and liberating time of life with the proper expectations. Talk to normal emergency physicians who have done it to find out more.

Mark L. DeBard, MD, FACEP
Columbus, Ohio

Retirement Comes

New fields, new hills, new roads,
Leading I know not where...But go I must!
Strange new sensations lurk in my heart.
Change is upon me!
This fiery feeling, a relentless flame,
To move on, to discover anew, to touch the worlds
I've never known.
Is it even too late?

In my gut there is a deep emptiness,
Not for nourishment
But for the life I so loved and cherished!
There is a heavy wave of loneliness, bewilderment
Sweeping over me, consuming me.
Where now is my sense of purpose?

Shay Bintliff, MD, FACEP
Kamuela, Hawaii

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Defending "Prudent Layperson" in Court

ACEP sues insurer for retroactive denials of emergency department visits

by LAURA WOOSTER, MPH; AND LESLIE PATTERSON MOORE, JD

In its escalating fight against Anthem BlueCross BlueShield's dangerous policy of retroactive denials of ED visits the insurer deems as "non-emergent," ACEP has taken legal action. Joined by the Medical Association of Georgia, ACEP filed a lawsuit against Anthem's BlueCross BlueShield of Georgia in July 2018 in federal court.

This action follows a yearlong effort by ACEP to protect the prudent layperson standard on behalf of its members and fight back against the policy that Anthem currently is enforcing in six states. These efforts have yielded significant progress: Anthem announced in February that it was expanding the "always pay exceptions" on the denials policy and would request a medical record for every potential denial; *The New York Times* ran a story on reactions to Anthem's policy that featured data contributed by ACEP on denials in each state the policy was implemented in; and most recently, Sen. Claire McCaskill (D-MO) published a report on the Anthem issue for which ACEP also contributed information.

But even with Anthem's changes to the policy, lives are still being endangered merely by its continued existence. Anthem policyholders are still being told by the insurer to "save the ER for emergencies, or you'll be responsible for the cost." Yet, as we all know, it is often impossible for emergency physicians, much less patients, to know based on a patient's initial symptoms whether their condition will ultimately end up being emergent. Therefore, since Anthem continues to force patients to second-guess the decision to seek emergency care, ACEP and its leadership determined that further action was needed.

ILLUSTRATION: CHRIS WHISSEN PHOTOS: SHUTTERSTOCK.COM

ACEP's lawsuit asserts that Anthem's policy violates the prudent layperson standard, which requires insurance companies to cover the costs of emergency department visits based on a patient's symptoms and not the final diagnosis. Further, because the policy discriminates against those in protected classes, who utilize emergency departments more frequently and are disproportionally impacted by the financial stress created by having their claims denied, Anthem is also being sued for a violation of the 1964 Civil Rights Act. The lawsuit requests the court grant an injunction preventing Anthem from enforcing its destructive denial policy or retroactively denying benefits.

Stopping Anthem's retroactive ED denials policy with this lawsuit is critical to protecting the prudent layperson standard and working to ensure other payers do not follow with their own similar dangerous policies. ACEP is currently also fighting back against BlueCross BlueShield of Texas' new policy to deny coverage for its HMO patients who seek care for what it deems as non-emergent conditions at an out-of-network facility, as well as Medicaid managed care plans and state waiver applications that also erode the prudent layperson standard. ACEP continues to engage in efforts with federal policymakers to strengthen that standard and ensure it is appropriately enforced, as required under federal law.

MS. WOOSTER is ACEP's associate executive director of public affairs. **MS. MOORE** is ACEP's general counsel.

TOXICOLOGY Q&A

Berry Dangerous

PHOTO: JASON HACK (OLEANDER PHOTOGRAPHY)

by JASON HACK, MD

QUESTION: Can this blueberry-esque toxin be used to treat certain illnesses?

ANSWER *on page 8*

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PHOTO: JASON HACK (OLEANDER PHOTOGRAPHY)

POKEWEED

Phytolacca americana

COMMON NAMES: **Poke, pokebush, pokeberry, pokeroot, poke sallet, inkberry, cancer root, American nightshade, pigeon berry.**

Toxicology Q&A Answer

ANSWER: Yes. Pokeweed has been shown in nonhuman studies to have anti-tumor properties and to have activity against herpes viruses and HIV.

Toxins

All parts of the mature pokeweed plant contain toxins, but the root is most toxic. The effects of this plant on biological systems are many due to the large number of toxins present. These include:

- **Alkaloids:** betanidine, betanine, phytolaccine, and prebetanine
- **Lectins:** pokeweed mitogen glycoproteins
- **Saponins:** phytolaccosides, jaligonic acid, phytolaccagenic acid, and aesculentic acid
- Isoamericanin A
- Pokeweed antiviral protein (PAP)
- Alpha-spinasterol
- Histamine
- GABA phytolaccatoxin and related triterpene saponins

Symptoms

Ingestion can cause nausea, vomiting, diarrhea, abdominal cramps, headaches, blurred vision, confusion, dermatitis, dizziness, and weakness. Convulsions, low blood pressure, rapid heartbeat, heart block, and death may occur. Children have been poisoned by eating raw pokeweed berries, and although rare, death may occur.

Facts

Used by Native Americans as an herbal cure, pokeweed has been found to contain PAP, which has anti-tumor effects in mice and laboratory studies.

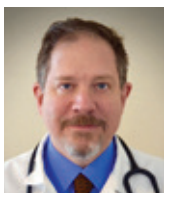
Pokeweed mitogen (mitogens are substances that stimulate cell division, or mitosis) is a lectin that causes both an increase in the numbers of lymphocytes and erythrocyte agglutination (clumping). These glycoproteins are used to study white blood cell function.

In test tube studies, PAP has also shown action against viruses such as herpes and HIV. Clinical trials have not yet determined whether these effects are seen in humans.

Young pokeweed shoots, which contain very low levels of toxins, are eaten as poke salad (poke salat) in traditional southern U.S. cuisine. It is thoroughly boiled in water that is changed twice during cooking to remove the toxins.

Pokeweed is found growing wild throughout many areas of the United States.

It goes through a rainbow of colors during its maturation. Young fruiting stems are initially white with green buttons. Fruits become mottled and finally turn black while the stems turn a striking red-pink color. All of this is contrasted by deep green leaves.



DR. HACK (OLEANDER PHOTOGRAPHY) is an emergency physician and medical toxicologist who enjoys taking photographs of beautiful toxic, medicinal, and benign flowers that he stumbles upon or grows in his garden. Contact him at ToxInRI@gmail.com.

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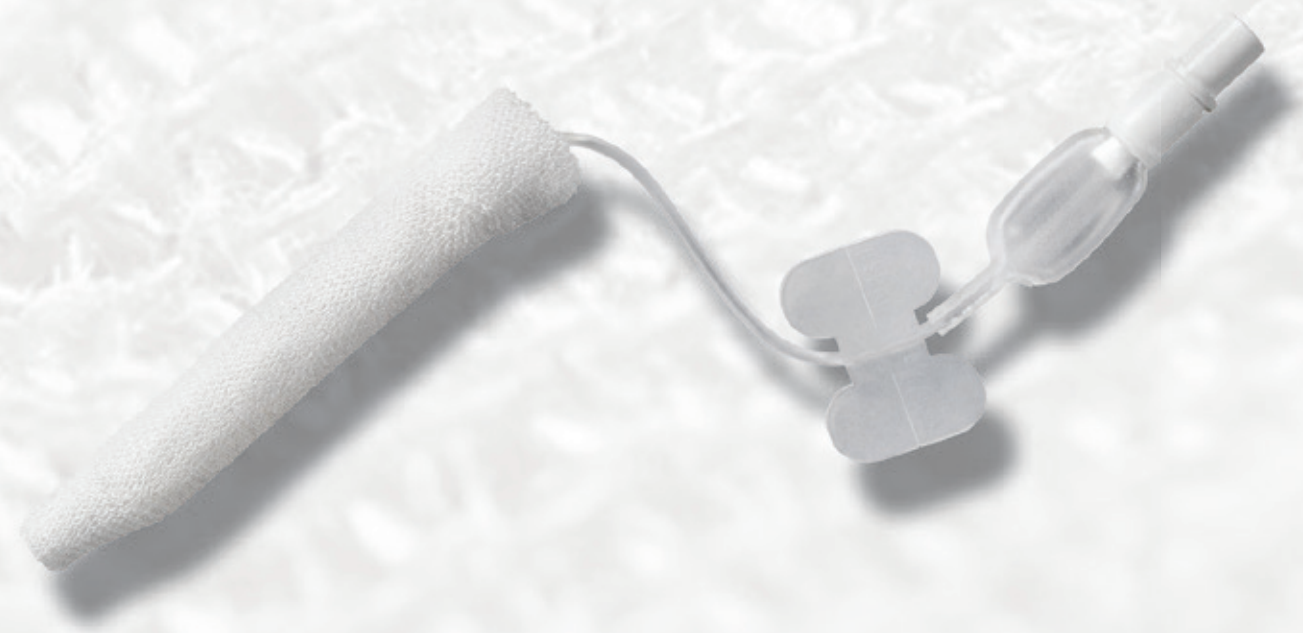

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PHOTOS: ACEP

ABOVE: Dr. Greg Henry

LEFT: Dr. Henry speaks with ACEP members after a presentation.

BELOW & OPPOSITE PAGE: Dr. Henry speaking at past ACEP meetings.

ob-gyns, etc., who took their turn in the barrel once every month or so. People were starting to realize that was the wrong way to do it. The first critical hour was where emergency care should concentrate its efforts.

KK: Knowing the criticisms that those initial founders received, what are some of the foundational pieces that helped us to be recognized and respected as a specialty?

GH: The first hurdle was psychological. You had to believe you were as good a doctor as anyone else. The second was that we needed a reasonable training process. The third thing was the first board examination in emergency medicine. We did it better than any other board at that point in time. We really looked at how questions were framed. Were they true discriminators of knowledge, and did they predict success, producing better doctors?

When we moved from being a conjoint board with family practice to a fully independent board, we'd come of age as the 23rd specialty board in the United States.

KK: Is there anything that either helped solidify the foundation of emergency medicine or attempted to destabilize it?

GH: There was no specialty that ever grew as fast as emergency medicine. People saw that it was an intellectual challenge, needing excellent people. The paradox was that excellent people were needed in cities, which weren't prominent academically. We were needed where the patients were, as one of the first specialties that was truly patient-centered.

As health care becomes more and more complex, our role in resource management and guiding policy is only going to increase.

This reflects what citizens of the United States need to receive better health care.

KK: Greg, you've been described as the junkyard dog of emergency medicine, because you defended us tirelessly. Do you have a personal story you can share?

GH: One humorous story is about my daughter marrying the son of the chairman of radiology at Duke. This was, at first, an unholy alliance [emergency medicine and radiology], as might be expected. However, as we got more and more into this, the chairman, following insurmountable pressure, made sure that their ultrasonography people were going to train the emergency medicine residents exactly the same as he did the radiology residents. Perhaps, this helped to lessen some political barriers in training and access to point-of-care ultrasound.

As ACEP President, I represented us at the American College of Surgeons. Everyone sitting on the other side of the table from us was a professor at an ivory tower program. Almost none of them actually primarily saw patients. I pointed out, "The thing that you're most afraid of is us taking your jobs, which is exactly what the surgeons want us to do in the community. They don't want to be running in for anything unless they're about to take them to the operating room."

After we got our barbs, comments, and Shakespearean quotes out, they said, "You know, you may have something there and it may be important." In the old days, all the trauma resuscitation stuff was under the control of surgery. Interestingly, that wasn't

where the surgeons were doing most of their research. Emergency physicians were initially caring for trauma in this country.

KK: Those who do not recognize history are doomed to repeat it. Do you see us revisiting history?

GH: We went from, early after the Second World War, seeing 20 million emergency visits to now something around 140 million visits or more. We can't rest on our laurels. We've built a specialty, but the work of the next half century is just beginning. Innovative care models are being contemplated and designed. I think that our people are superbly trained and experienced to handle many of these situations [eg, telemedicine]. If we don't pursue this with the same vitality, we can be sucked up and blown away with the tide of history by other people who want to get into these areas as well.

I'm spending time with people who are looking at health care in America and why it's costing us two or three times more to take care of patients than it costs elsewhere. They are asking important questions, which we should be anticipating. We need to be on the side of history, figuring out how to provide better care for less money, with less utilization of expensive technology.

KK: Where do you see emergency medicine in the future?

GH: We are going to have to evaluate the medical educational system. Many countries in the world do not send you for four years to get a degree before you start your medical training. What role will [physician assistants, nurse practitioners, emergency medical technicians,] etc.] play, and how should we guide this? I see emergency physicians of the future being more involved in thinking and providing opinions than just sewing up wounds. For example, physicians don't need to repair most lacerations. The business world and consumers will continue to pose questions of value that we must be prepared to answer.

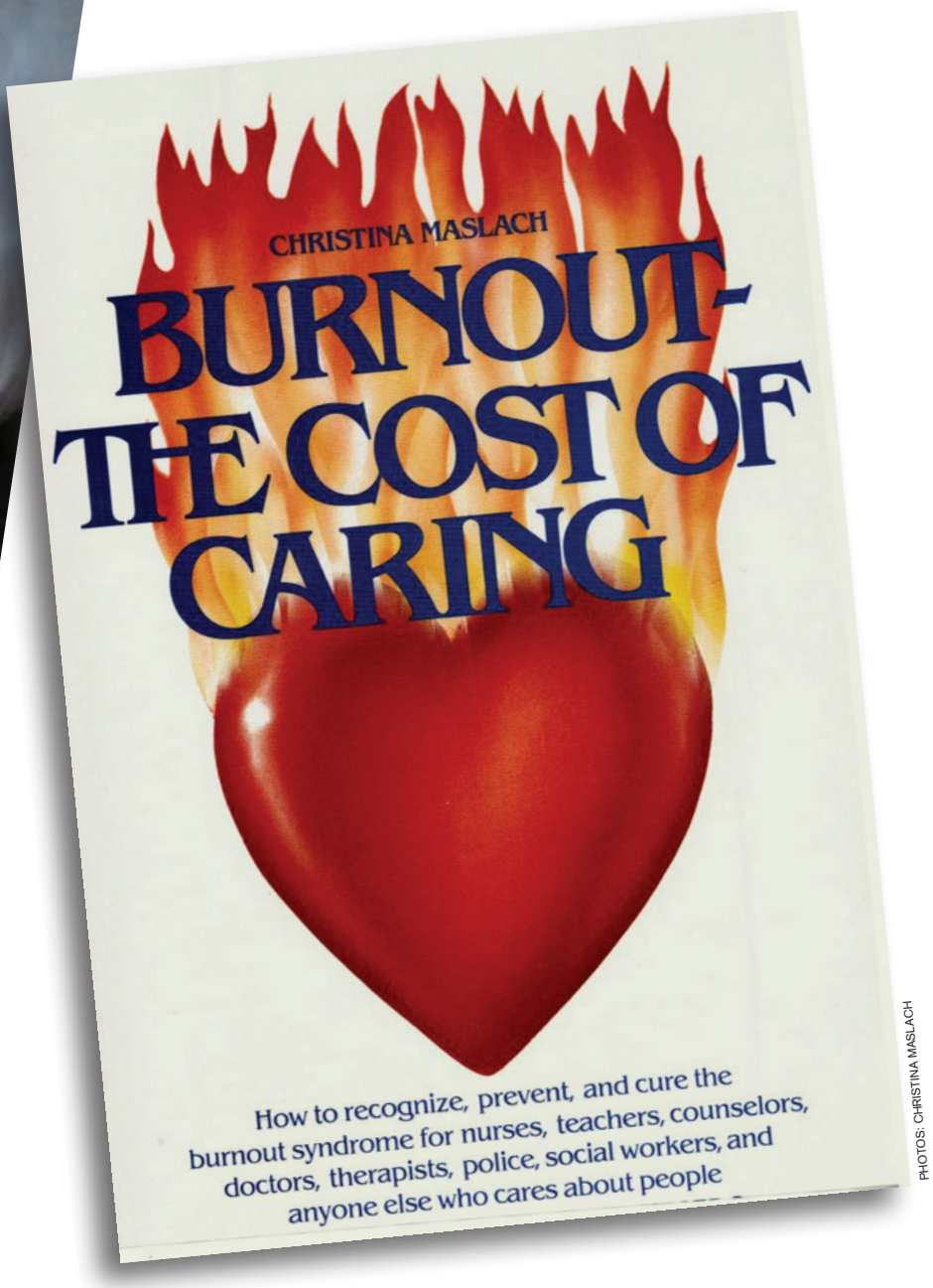
KK: Any words of wisdom for younger emergency physicians for a successful and fulfilling career?

GH: The best way that the young physician coming up can handle burnout is to like what you do for a living. I love my work and always have.

I think we need to start programming and help our young docs program themselves to have a logical progression of their career. You start out on midnights wrestling intoxicated patients. You may end up running a telemedicine service that covers half the state of Montana. The way we fight burnout and this feeling that we're not accomplishing anything is to always have another goal, something we're going to do to expand and revitalize our careers.

KK: Greg, any final thoughts?

GH: Well, I go back a long time. As you remember, I took care of Lincoln and that didn't go well. If we become entrenched in how we do things without looking ahead to ask new questions, and we can't define the goal as improving health care, then we're on a road to nowhere. If we continuously look at what actually makes a difference in how patients turn out, then we're going to be where we need to be to have both the American people and the house of medicine on our side.



PHOTOS: CHRISTINA MASLACH

LEFT: Image from the cover of the issue of *Human Behavior* magazine where Dr. Maslach published her first article in 1976.

RIGHT: Cover of *Burnout: The Cost of Caring,* published in 1982.

The Roots of Burnout: Part 1

DR. CHRISTINA MASLACH'S PIONEERING RESEARCH GAVE US A WAY TO MEASURE BURNOUT

When Christina Maslach, PhD, started her psychology research career in the early 1970s, she didn't know that her work would lead to the Maslach Burnout Inventory, a measure for professional burnout that's still being used today. She first published the inventory with coauthor Susan E. Jackson in 1981. Dr. Maslach, who is professor of psychology at the University of California, Berkeley, has researched and published extensively about burnout throughout her career, and has helped to define the way we discuss and understand the combination of stress, exhaustion, and powerlessness that endangers the careers—and lives—of many emergency physicians.

ACEP Now Medical Editor-in-Chief Kevin Klauer, DO, EJD, FACEP, recently sat down with Dr. Maslach to discuss the early research that led to her developing the Maslach Burnout Inventory and what she's learned from decades of talking to people about burnout. Here is Part 1 of their conversation. Part 2 will appear in the October issue.

KK: Tell us how your background led you to work on this particularly important topic.

CM: I received a PhD in social psychology from Stanford University, and then I took a job at the University of California at Berkeley, where I've been for the rest of my career. I had done research on emotion while I was in the doctoral program, particularly focusing on how people dealt with some of the emotional challenges or crises they might experience.

At Berkeley, I wasn't able to start doing my research because they hadn't yet provided me with a research facility. So, I thought I'd go and interview some people who might give me some insight into their experience. From that, I would develop some hypotheses and research and so forth. I started interviewing some people who I thought might face these kinds of emotional challenges. I was talking with, in terms of health care, for example, physicians who were working in emergency departments, with oncology wards, and nurses—and people would keep referring me to somebody else—just talking to psychiatric nurses, police officers, ministers, and different people who sometimes had some very difficult situations.

What I found in the interviews was very serendipitous. I had never heard about burnout. I wasn't talking about burnout, but what was happening in the interviews is that people would say, "Here's what's happening. I know this is confidential, so I've never really said much about it to anybody, but ..." Then they would be describing their particular story, and what I found was there was a kind of a rhythm to the story; there were some fairly common themes.

One day, I was talking with someone who had been working in poverty law, and she said, "That sounds familiar. I don't know what they call it elsewhere, but we call it burnout." I would ask people at the end of the interview if they ever describe this to other people, and if so, how did they talk about. I never got much of an answer.

I described some concepts that appear in sociology, psychology, health literature, and they'd say, "No, no, no." Then I added, "So, what about burnout?" "Yeah, that's it, oh my gosh." What I was finding was it was really not a psychological concept, but it was something that was really a grassroots sort of thing. The people themselves said this term captured what they were feeling. After that I would use "burnout" at the end of the interview to talk with them about it.

KK: What time frame was this?

CM: This was in the early to mid '70s.

KK: Did this prompt you to then do the survey?

CM: Yes. All of that work came out of this original experience. I was doing interviews with different people, and then when possible, I would observe them at work to see what their work day was like. I talked to their colleagues, or we talked to spouses of these people. We were trying to get a sense from people who knew this person, worked with them, and maybe shared the same kind of experiences. Although it wasn't something that I had intended to do, or that I set out with a mission to define burnout, but once I stumbled over it, it was clear that there was something really important about this.

I had a hard time getting published at first. It wasn't laboratory research like I had been trained to do. My first article about this was written for a popular magazine called *Human Behavior*. They published it in 1976, and in an interesting way, that was maybe a better spot for all of the things I did on burnout because that generated tons of feedback. These were snail mail days. Tons of letters and phone calls. People would say, "Oh my gosh. I thought I was the only one. Let me tell you my story." I just felt I had stumbled upon something that was not well-known, not well-recognized. I was told it was pop psychology. People's experiences inspired me to continue this work, not to abandon other research I was doing, but to add this focus. After a while, it became more and more the main work that I was doing.

KK: Can you describe how hard it was and what the process was for you to develop the survey or the burnout inventory?

CM: The problem is that you have to develop a measurement that has evidence proving it is clearly measuring what it is that you say it's measuring.

It looks straightforward. People say, "Oh, it's easy. I'll just write a few questions of my own." Well, you have no idea if those questions are working correctly or not. There's something called face validity, which makes it sound right, but you need to gather other data to really test out which items, questions that you're using, and formats are really working well to measure what you say is being measured. Psychometric research took years and years of work by me, Susan Jackson, other students, and other colleagues because we had to gather data on so many

people in so many different ways to be able to triangulate on, proving that this was the thing that people were talking about [burnout].

I was fortunate because the professor in psychology who was one of the leading people in assessing psychological constructs was a member of my department, Harrison Golf. He really became my mentor, and made clear to me what it was that I had to do. It was really on-the-job training to do this. It took a long time, but it turned out well, in the sense of meeting all the criteria that you need for such a measure. Even though that was more than 40 years ago, it's still stood the test of time, and other measures that get developed are always comparing themselves to this standard. It surprises me a bit because I would have thought that people would have updated things or maybe come up with better options or done other sorts of things. I think all the work that we put in at that time has contributed to that.

KK: Did you have any idea that what you were developing would have the impact that it has today?

CM: No, not at all. I have to say, way back then, it wasn't only the editors of journals who would turn my articles away and not even read them because they said, "We don't publish pop psychology." It took a long time to get people to believe there was something there.

KK: Did you ever get discouraged?

CM: My interest in the topic really was stoked by the experiences of the people that I kept talking to over time, and that's true even now. I'd be interviewing people, and they were getting angry and upset, and they're crying. This was not something trivial. This really matters. People tell me stories about how this has affected their family and how they've made decisions they now wish they hadn't. It was something that fascinated me.

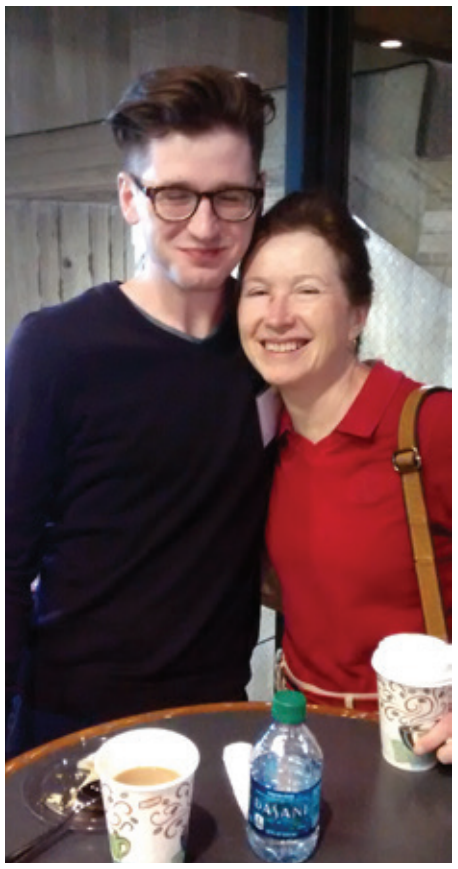
Dr. Christina Maslach

MARRIAGE & MEDICINE

Is a two physician marriage double the challenge or double the fun?

PHOTOS: THOMAS BENZONI & NOREEN O'SHEA

Dr. O'Shea and Dr. Benzoni at a recent conference.



Dr. O'Shea (**LEFT**) and Dr. Benzoni (**RIGHT**) with two of their children.

Being a physician can make relationships challenging—long hours, high stress, and the danger of burnout can tax even a strong marriage. But what happens when both spouses are physicians?

According to Noreen O'Shea, DO, FAAFP, and Thomas Benzoni, DO, FACEP, the challenges of their demanding careers are balanced by the understanding and support of being married to someone who knows exactly what it's like to provide care in the emergency department. The couple met as undergraduates and got married shortly before Dr. Benzoni started medical school. About 40 years later, they both teach part-time at Des Moines University in Des Moines, Iowa, where Dr. O'Shea also practices at a federally qualified health center and Dr. Benzoni practices at local emergency departments, Level 1 to Level 4.

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The couple recently sat down with *ACEP Now* Medical Editor in Chief Kevin Klauer, DO, EJD, FACEP, to discuss their experiences of being in a two-physician marriage.

KK: How long have you two been together?

NO: According to him, 50-plus years. We will be married 39 years in August.

KK: How did you two meet? Were you medical students?

TB: This goes back to Creighton University in a class on world hunger.
NO: We met when I was sophomore at Creighton. Everybody had to take a philosophy class, and so we were in a philosophy class on world hunger together.
TB: After our honeymoon, we could survive anything.
NO: We had a difficult honeymoon. We were camping on the Current River in southern Missouri and were attacked by horseflies and had a bout of Montezuma's revenge.
TB: Yeah. Don't give your wife salmonella poisoning on your honeymoon. That's the only advice I'll give you.
NO: We got married three weeks before he started medical school. And then I didn't start medical school until a year after him.

KK: Have you both always practiced emergency medicine?

TB: That's the only thing I know how to do. The chapter after Creighton is even more formative. Noreen was assigned with the Public Health Service to the Appalachian Mountains. We spent four years in Appalachia and built a hospital where there hadn't been one.
NO: I've been practicing family medicine, but I have done, in order to keep my skills up, one or two days a month in the emergency department.

KK: Tell us about the dynamic and intricacies of a two-physician marriage.

TB: To me, the big advantage is that Noreen understands that I'm in a 24-7-365 business and that sometimes when I come home, I'm a grumpy old bastard, and sometimes when I come home, it's been a really good day. Most of the days are in between.

KK: It has to be very helpful for somebody to have a fundamental understanding of what the environment is like and what the practice is like.

NO: It also started while we were in medical school. He understood when I felt like I had to study. And he could understand the stresses but also share in the joys.

KK: What are some of the challenges or obstacles of being together as a two-physician team?

TB: A challenge is the opposite side of an opportunity. Just going along chronologically, our oldest [our daughter] was born while we were in Michigan. Having children created some scheduling challenges. The department would have these Saturday morning meetings. Well, we both had to be there, so we'd bring her along. People looked at us funny because you didn't do that in those days. But we hadn't seen her all week, so she's coming with us anyway.

A lot of things just happened to work out if you were willing to get a little bit of grace back and forth. I still send Noreen my proposed schedule, and she gets to veto anything that she wants.

We tried for a while for each of us maintain our own calendars, and you can guess how that worked out. So she's in charge of the calendar.
NO: And sometimes if I didn't write it down or I made a mistake on the calendar, we would get a call an hour or half hour after the shift was supposed to have started, "Tom, where are ya?"
TB: In 35 years of doing that, that's only happened twice.

KK: Noreen, tell us about some challenges from your perspective.

NO: I don't type that well, so when I can't dictate because of the structure of the electronic medical record [EMR], I spend a lot more time

Dr. O'Shea and Dr. Benzoni at their wedding.

doing pajama time at home, charting on my patients. He doesn't have that luxury [to delay charting] in the ED the same way I do. Sometimes, he's aggravated about it, but he's more often my champion. We share frustrations about EMRs.

KK: It's difficult enough for someone to be with one physician, but both of you together as physicians in a relationship has to be very complicated. Did you ever get to the point where you thought it was just going to be too hard?

TB: I've always been a bit of a realist about it. I know I'm really hard to get along with, so I just figure, with a lot of forgiveness, it goes the other way, too.

NO: We did have a time that was really difficult. There was a lot of pressure externally when he was part of an independent group about 10 years ago. They got down to staffing a very busy Level 2 emergency department with four guys. That was really hard because he and all the rest of them were working so, so hard. That's a reason, among others, we moved to Des Moines to be out of that hot pressure-cooker situation where he was taking on so much responsibility and so many shifts.

KK: It sounds like that was a turning point for you, too, that if it continued, it could have put your relationship in jeopardy?

TB: By then, the kids were gone. They were all out of the house, and I didn't see any reason to keep working that hard either. Maintaining the relationship is so important. I often tell people—they think I'm being snarky about it, and it's only partly true—39 years of marriage and not having to pay a divorce lawyer really gives us a lot of freedom.

NO: I feel like, as a family physician, I can defend emergency physicians and how difficult their work is because not only do I live with one and see that, but I also have worked in the emergency department. Part of my role as a physician's spouse is to represent my spouse's specialty in a positive manner. He has also done the same thing.

KK: Can you offer a couple of thoughts for people who may be earlier in their relationships? If you're going be with a physician or if you're going to be in a two-physician relationship, how can you make that work?

TB: For me, it's really easy. Bring in the same attitude you do to work. You have to learn to live, and you have to learn to give some and deemphasize yourself. If you're fighting, you're probably not fighting for anything important anyway.

NO: We would make sure we'd get to the kids' games or whatever was happening at school. He was able in his group to arrange the schedules so that any of his partners or he could make it at the beginning or the end of the school play. Making time for each other and family is really important.

We also find great joy in being part of local medical societies and supporting other physician couples or even couples that are one physician and a non-physician spouse. That has been really helpful.

KK: How many kids do you have?

TB: Want some? Four of them.

KK: I'm sure you wouldn't give any of them up. How old are they?

NO: One is 33. She'll be 34 in September. The rest are 30, 28, and 25. Our 28-year-old is in her EM residency.

KK: I've learned from listening to you two that despite the fact that it can be challenging in any relationship, you have to find ways to make it work, to find the positives, and to overcome the negatives. You two have been very successful in doing that. Thank you very much for your time and congratulations on all of your successes.

REBECCA PARKER, MD, FACEP
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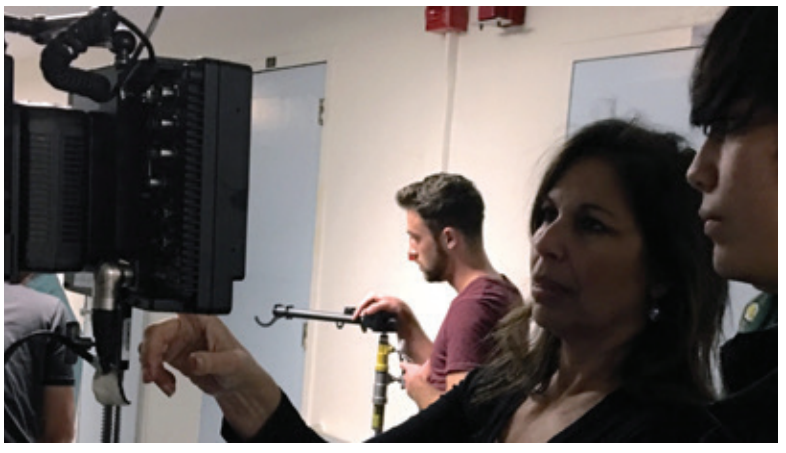
THE MAKING OF DO NO HARM

Behind the scenes of a film on the taboo topic of physician suicide and depression

by CHRISTOPHER I. DOTY, MD, FAAEM, FACEP; AND ROBYN SYMON

PHOTOS COURTESY: SYMON PRODUCTIONS, INC.



TOP: Scene from ***Do No Harm.***

LEFT, BOTTOM: Filmmaker Robyn Symon on the set of ***Do No Harm.***

LEFT, TOP: Physicians promote a petition asking AAMC and ACGME to take action to prevent medical student and resident suicides.

ABOVE: Poster from ***Do No Harm***.

As the camera pans on an aerial shot of the New York City skyline at dusk, we hear the desperate voice message of a doctor inside Mount Sinai Hospital revealing a colleague has just jumped off the building. "This keeps happening and they're just trying to cover it up."

It's the opening scene of the new documentary film *Do No Harm* by Emmy-winning producer Robyn Symon, who pulls back the curtain of the hidden epidemic of physician suicide and depression among doctors and medical students.

"Someone sent me an article about two residents who jumped off the roof of their hospitals in 2014," says Ms. Symon, who comes from a family of physicians. "I know what it takes to make it through medical school, so I needed to know why someone who had sacrificed so much would want to end it all."

More recently, in May 2018, a medical student and a resident at New York University took their lives, putting everyone on edge. This is not uncommon; almost every physician knows a physician who has committed suicide. In fact, physicians have one of the highest rates of suicide among all professions and almost twice the rate of the general public. Emergency physicians are at or near the top of the list. According to the American Foundation for Suicide Prevention, an estimated 400 physicians take their lives every year, but the number is believed to be much higher since many suicides are reported as accidental deaths.

Bullying, sleep deprivation, burnout, the lack of autonomy, and the inability to seek emotional help for fear it could jeopardize a career have created a ticking time bomb. More than 50 percent of attending physicians and over 60 percent of trainees report suffering from burnout. How medical schools and hospitals have responded to this crisis has been disappointing to say the least, turning a blind eye to protect their reputations and reduce the risk of liability.

Overcoming Stigma and Suppression

Due to the stigma associated with mental health, finding physicians to talk about this crisis proved to be a big challenge for the filmmaker. The first person Ms. Symon reached out to was Pamela Wible, MD, a family physician who runs a hotline out of her house in Eugene, Oregon, for suicidal physicians and medical students. Dr. Wible, whose TEDMED talk on physician suicide has been viewed more than 400,000 times, has been on a mission to shine a light on this taboo topic. She connected the filmmaker to many physicians and others whom Ms. Symon and her crew followed for more than a year. Woven into the film are interviews with medical students, senior physicians, authors, sleep experts from Harvard Medical School, and leaders from medical organizations such as the American Medical Association, Association of American Medical Colleges (AAMC), and Accreditation Council for Graduate Medical Education (ACGME).

"Many practicing physicians have suppressed their experiences from medical school, but it's laid the foundation for an unhealthy, disconnected, wounded healer syndrome that physicians have learned to cover up very well," says Ms. Symon. "Especially surgeons and ED physicians who experience life and death every day, yet are offered no coping skills. It's like suffering from PTSD."

The impact of our assembly-line health care system is taking a toll on practicing physicians. Many self-medicate, which can lead down the slippery slope to addiction. Others retire early, which has led to very real doctor shortages. "A perfect storm is brewing," says Ms. Symon. "You have baby boomers relying more and more on a health care system where more and more disillusioned doctors are headed for the exit."

The film delves into the link between sleep deprivation and medical errors where Harvard sleep expert Charles Czeisler, MD, says residents and physicians working marathon shifts are set up to fail.

Many hospitals are adding wellness programs, but the film contends what's really needed is an overhaul of the medical training system and state medical licensing boards. In many states, physicians must disclose whether they've ever sought emotional help, forcing many physicians to hide treatment and lie or self-medicate to obtain a medical license.

Starting a Dialogue on Suicide

The film, completed in June 2018, took four years to make and will be launching an international film tour in the fall, which will include screenings at hospitals, medical schools, and conferences, including ACEP18.

The goal of the film is to open a dialogue in the medical community about a crisis that's been covered up for decades and discuss solutions and there are some promising signs that change is afoot. As Darrell Kirch, MD, President and CEO of the AAMC says in the film, "we have to take care of ourselves if want to take the best care of our patients." The simple truth is we can't afford to keep losing talented physicians to depression and suicide.

To watch the trailer and for information on the film, visit www.DoNoHarmFilm.com

DR. DOTY is professor and vice chair for education at the University of Kentucky in Lexington.

MS. SYMON is the director and producer of *Do No Harm*.

Watch at ACEP18!

There will be a screening of "Do No Harm" Tuesday, Oct. 2, 5:30-7:30 p.m., in room 25B of the San Diego Conference Center.

2018–2019 EMERGENCY PHYSICIAN COMPENSATION REPORT

The national average climbed again, but wide variations exist state to state

by BARB KATZ

THE national average salary for emergency physicians increased again this past year, a full 3.5 percent. Not a stunning number, but when you add it into the trend of the past 10 years, it reflects a 34.5 percent increase for emergency physician salaries over the past 11 years.

How is it happening? States that have been chronically low-paying historically are starting to climb. In New York, for instance, starting salaries increased 25 percent this year. Even the West saw dramatic increases, with salaries up 32 percent in Nevada and 14 percent in New Mexico.

The Midwest continues to be all over the map, with increases in Michigan (11 percent), Minnesota (12 percent), and Ohio (14 percent) and a big decrease in Kansas of 18 percent. The Mid-Atlantic states experienced a 17 percent increase overall, including a 20 percent hike in the District of Columbia. The Pacific Northwest posted a 15 percent increase in Montana and 14 percent in Washington.

Another important number is the percentage of job opportunities open to physicians with primary care board certification (PC-BC). Currently, this is 43 percent! With nearly half the country's emergency medicine jobs open to physicians not trained in emergency medicine, we have further evidence of the location-driven supply and demand market in the specialty. I see this number increasing in the next five years.

Trends and developments this year include:

- Urgent care salaries are creeping up and, in some cases, pay as much or even more than emergency physician incomes in some states.
- Sign-on bonuses continue to grow, with $50,000 a norm and a high between $120,000 and $150,000 in geographically challenged areas.
- Broad salary ranges continue in some states, such as $116–$300 an hour in Pennsylvania and $160–$282 an hour in Minnesota.
- The highest dollars in emergency medicine occur in locum tenens offers, with the $300–$320 an hour appearing more frequently. I even found one location offering $350 an hour in North Dakota.
- Only eight states provide no options for PC-BC physicians this year.

The following numbers are based on working 1,632 clinical hours a year and include incentive bonuses and relative value unit compensation, where applicable. Annual package numbers include basic benefits valued at $30,000. Sign-on bonuses, loan assistance, and other perks are not included. Rankings are based on state averages, not highs and lows.

THE SOUTHEAST once again leads the country with a regional average of $236 per hour/$416,000 a year. It also nearly leads the country in opportunities open to physicians with PC-BC at 54 percent, up 26 percent from last year.

MISSISSIPPI: Average: $265/hr., $463,000 ann.; 50% PC-BC; high of $300/hr.; *no change*

SOUTH CAROLINA: Average: $253/hr., $444,000 ann.; 54% PC-BC; high of $500,000 ann.; *up 7%*

GEORGIA: Average: $238/hr., $418,000 ann.; 71% PC-BC; high of $300/hr.; *up 6%*

TENNESSEE: Average: $234/hr., $412,000 ann.; 75% PC-BC; no real highs; *no change*

ALABAMA: Average: $234/hr., $412,000 ann.; 25% PC-BC; high of $500,000 ann.; *up 10%*

NORTH CAROLINA: Average: $228/hr., $402,000 ann.; 51% PC-BC; no real highs; *up 8%*

ARKANSAS: Average: $226/hr., $400,000 ann.; 100% PC-BC; no real highs; *no change*

LOUISIANA: Average: $225/hr., $397,000 ann.; 33% PC-BC; no real highs; *down 7%*

FLORIDA: Average: $225/hr., $397,000 ann.; 25% PC-BC; high of $350/hr.; *no change*

THE SOUTHWEST/WEST comes in second with a regional annual average of $220 per hour/$389,000 a year, up 10 percent from last year. Opportunities open to physicians with PC-BC are at 50 percent, up 8 percent.

NEW MEXICO: Average: $271/hr., $472,000 ann.; 50% PC-BC; high of $533,000 ann.; *up 14%*

NEVADA: Average: $248/hr., $434,000 ann.; 40% PC-BC; no real highs; *up 32%*

TEXAS: Average: $247/hr., $434,000 ann.; 43% PC-BC; high of $320/hr.; *down 9%*

CALIFORNIA: Average: $228/hr., $402,000 ann.; 52% PC-BC; high of $520,000 ann.; *no change*

ARIZONA: Average: $218/hr., $386,000 ann.; 53% PC-BC; high of $500,000 ann.; *no change*

OKLAHOMA: Average: $203/hr., $362,000 ann.; 70% PC-BC; high of $500,000 ann.; *no change*

HAWAII: Average: $180/hr., $324,000 ann.; 0% PC-BC; no real highs; *no change*

COLORADO: Average: $165/hr., $300,000 ann.; 40% PC-BC; high of $210/hr.; *no change*

UTAH: *No jobs open or information available*

THE 13 STATES of the Midwest have a $212 per hour/$377,000 a year regional average, with 52 percent of the jobs open to physicians with PC-BC.

NORTH DAKOTA: Average: $233/hr., $410,000 ann.; 0% PC-BC; high of $350/hr. (locum tenens); *no change*

ILLINOIS: Average: $232/hr., $408,000 ann.; 45% PC-BC; high of $500,000 ann.; *up 5%*

OHIO: Average: $231/hr., $407,000 ann.; 56% PC-BC; high of $312/hr.; *up 14%*

KENTUCKY: Average: $230/hr., $405,000 ann.; 66% PC-BC; high of $487,000 ann.; *down 3%*

INDIANA: Average: $230/hr., $405,000 ann.; 50% PC-BC; no real highs; *no change*

WISCONSIN: Average: $215/hr., $380,000 ann.; 53% PC-BC; high of $520,000 ann.; *no change*

MISSOURI: Average: $206/hr., $367,000 ann.; 52% PC-BC; no real highs; *no change*

MINNESOTA: Average: $201/hr., $358,000 ann.; 58% PC-BC; high of $489,000 ann.; *up 12%*

MICHIGAN: Average: $196/hr., $350,000 ann.; 76% PC-BC; no real highs; *up 11%*

IOWA: Average: $195/hr., $348,000 ann.; 55% PC-BC; no real highs; *up 6%*

KANSAS: Average: $193/hr., $344,000 ann.; 66% PC-BC; no real highs; *down 18%*

NEBRASKA: Average: $190/hr., $340,000 ann.; 45% PC-BC; no real highs; *no change*

SOUTH DAKOTA: *No jobs open or information available*

FOR THE FIRST TIME, THE PACIFIC NORTHWEST is fourth regionally instead of last, with an average of $200 per hour/$357,000 a year due to increases in Montana and Washington. PC-BC acceptance is 62 percent, doubled from last year.

WYOMING: Average: $228/hr., $402,000 ann.; 64% PC-BC; no real highs; *no change*

IDAHO: Average: $223/hr., $393,000 ann.; 66% PC-BC; high of $300/hr.; *no past information*

MONTANA: Average: $194/hr., $346,000 ann.; 25% PC-BC; no real highs; *up 15%*

OREGON: Average: $182/hr., $328,000 ann.; 52% PC-BC; no real highs; *no change*

WASHINGTON: Average: $175/hr., $315,000 ann.; 90% PC-BC; no real highs; *up 14%*

ALASKA: *No jobs open or information available*

THE SEVEN MID-ATLANTIC STATES come in under the national average at $198 per hour/$353,000 a year, with 29 percent of jobs open to PC-BC.

VIRGINIA: Average: $243/hr., $426,000 ann.; 38% PC-BC; no real highs; *up 3%*

PENNSYLVANIA: Average: $218/hr., $387,000 ann.; 50% PC-BC; high of $520,000 ann.; *no change*

NEW JERSEY: Average: $204/hr., $362,000 ann.; 32% PC-BC; no real highs; *up 9%*

WEST VIRGINIA: Average: $194/hr., $346,000 ann.; 60% PC-BC; no real highs; *no change*

MARYLAND: Average: $184/hr., $330,000 ann.; 25% PC-BC; no real highs; *up 10%*

DISTRICT OF COLUMBIA: Average: $175/hr., $314,000 ann.; 0% PC-BC; no real highs; *up 20%*

DELAWARE: Average: $165/hr., $300,000 ann.; 0% PC-BC; high of $250/hr. (locum tenens); *no change*

IN LAST PLACE, THE NORTHEAST continues to drag its feet with a regional average of $186 per hour/$333,000 a year, despite the 25 percent hike in New York salaries. However, this region leads the country with the fewest opportunities for PC-BC at only 13 percent.

NEW YORK: Average: $208/hr., $370,000 ann.; 37% PC-BC; high of $479,000 ann.; *up 25%*

MASSACHUSETTS: Average: $186/hr., $333,000 ann.; 0% PC-BC; no real highs; *no change*

VERMONT: Average: $184/hr., $330,000 ann.; 0% PC-BC; no real highs; *no change*

MAINE: Average: $180/hr., $324,000 ann.; 25% PC-BC; no real highs; *no change*

CONNECTICUT: Average: $179/hr., $322,000 ann.; 0% PC-BC; high of $275/hr. (locum tenens); *no change*

NEW HAMPSHIRE: Average: $178/hr., $320,000 ann.; 15% PC-BC; high of $400,000 ann.; *no change*

RHODE ISLAND: *No jobs open or information available*

Figure 1. States Offering the Most and Least Compensation

TOP 10 STATES FOR COMPENSATION

1. New Mexico
2. Mississippi
3. South Carolina
4. Nevada
5. Texas
6. Virginia
7. Georgia
8. Tennessee
9. Alabama
10. North Dakota

BOTTOM 10 STATES FOR COMPENSATION

1. Colorado
2. Delaware
3. District of Columbia
4. Washington
5. New Hampshire
6. Connecticut
7. Maine
8. Hawaii
9. Oregon
10. Maryland

MS. KATZ is president of The Katz Company EMC, a member of ACEP's Workforce and Career sections, and a frequent speaker and faculty at conferences and residency programs. Contact her at katzco@cox.net.

Council to Consider Physician Suicide, the Opioid Crisis, Violence, and More

HIGHLIGHTS FROM THE RESOLUTIONS BEING CONSIDERED AT ACEP18

At the ACEP18 Council meeting, resolutions brought forward by members of the College will be discussed. These resolutions, the discussions, and the voting by the Councillors help to lay the path for ACEP's future.

Here are 10 of the 51 resolutions being brought before the ACEP18 Council meeting. For a full list, please visit acep.org/council.

- No More Emergency Physician Suicides
  Pennsylvania College of Emergency Physicians
- Advocacy for Expansion of Residency Positions to Address the Looming Physician Shortage
  New York Chapter
- Funding for Buprenorphine-Naloxone Treatment Programs
  Yemi Adebayo, MD
  Arjun Chanmugam, MD, FACEP
  Kyle Fischer, MD, FACEP
  Maryland Chapter
- Funding of Substance Use Intervention and Treatment Programs
  Yemi Adebayo, MD
  Arjun Chanmugam, MD, FACEP
  Kyle Fischer, MD, FACEP
  Maryland Chapter
- Generic Injectable Drug Shortages
  Rick Blum, MD, FACEP
  Mark DeBard, MD, FACEP
  Nicholas Jouriles, MD, FACEP
  West Virginia Chapter
- Violence Is a Health Issue
  Trauma and Injury Prevention Section
- Antimicrobial Stewardship
  California Chapter
  Washington Chapter
  Wisconsin Chapter
- Care of Individuals with Autism Spectrum Disorder in the Emergency Department
  Pennsylvania College of Emergency Physicians
- Supporting Medication for Opioid Use Disorder
  Pain Management and Addiction Medicine Section
  Social Emergency Medicine Section
  Washington Chapter
- Surreptitious Recording in the Emergency Department
  Emergency Medicine Informatics Section

ACEP17 Council meeting.

PHOTO: ACEP

2019 Proposed Rule

WHAT'S IN STORE FOR EMERGENCY MEDICINE?

BY MICHAEL A. GRANOVSKY, MD, FACEP, CPC

The 2019 Medicare Physician Fee Schedule Proposed Rule was released on July 12, 2018, and it includes significant proposed changes from the Centers for Medicare and Medicaid Services (CMS) relevant to emergency medicine. ACEP has submitted robust commentary on it. The Final Rule should be released in November and go into effect Jan. 1, 2019.

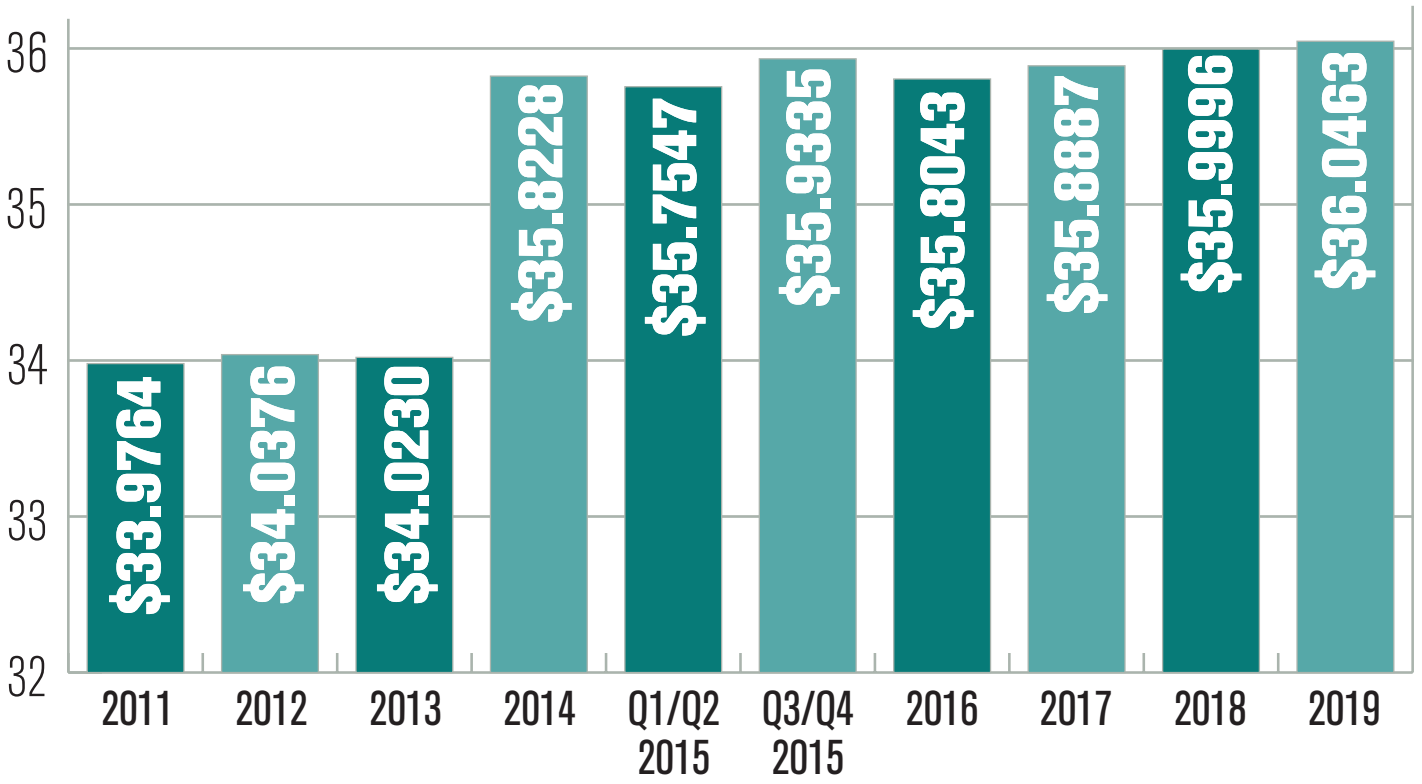
Here are some emergency medicine–related highlights from the Proposed Rule.

RVU Remains Stable

Each year, based on several technical formulas, CMS publishes the Medicare reimbursement rate per relative value unit (RVU, ie, the conversion factor). Many private payers then incorporate the Medicare changes when considering their own rates, so this conversion factor has far-reaching economic implications.

The proposed 2019 conversion factor of $36.0463 represents a slight increase from 2018's $35.9996. Following a low point in 2011, the conversion factor has generally increased and is no longer governed by the flawed Sustainable Growth Rate formula (see Figure 1).

Figure 1: CMS Payment Per RVU



The RVU Value of ED Codes

At the end of last year, the 2018 Physician Final Rule highlighted concerns that emergency department evaluation and management (E/M) services may be undervalued:

"We received information suggesting that the work RVUs for emergency department visits did not appropriately reflect the full resources involved in furnishing these services. We agree with the majority of commenters that these services may be potentially misvalued given the increased acuity of the patient population. As a result, we look forward to reviewing the RUC's recommendations regarding the appropriate valuation of these services for our consideration in future notice and comment rulemaking."

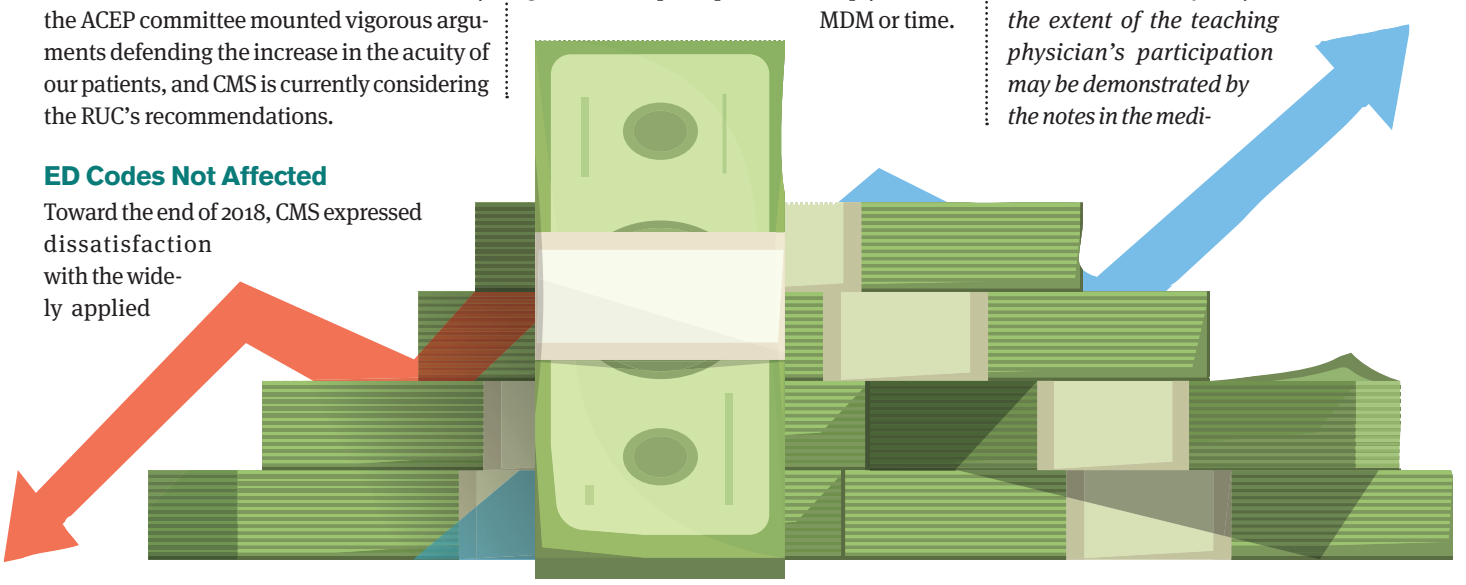
ACEP's Relative Value Update Committee recently presented the ED E/M codes (99281–99285) that make up 83 percent of our RVUs for valuation by the Relative Value Scale Update Committee (RUC). Although the RUC's deliberations remain confidential, I can say the ACEP committee mounted vigorous arguments defending the increase in the acuity of our patients, and CMS is currently considering the RUC's recommendations.

ED Codes Not Affected

Toward the end of 2018, CMS expressed dissatisfaction with the widely applied 1995 Documentation Guidelines for Evaluation and Management Services, stating they may not reflect today's more electronic clinical documentation processes:

"The guidelines have not been updated to account for significant changes in technology, especially electronic health record (EHR) use, which presents challenges for data and program integrity and potential upcoding, given the frequently automated selection of code level. In the near-term, it may be possible to eliminate the current focus on details of history and physical exam, and allow MDM [medical decision making] and/or time to serve as the key determinant of E/M visit level."

For 2019, CMS has proposed significant changes to the documentation guidelines for the office visit/urgent care codes but has elected *not* to apply these changes to the more complex ED environment. The new patient and the established patient office visit codes would be collapsed for levels 2–5, with a single payment rate and the ability for the provider to choose the current 1995 documentation guidelines or perhaps score it simply based on MDM or time.



ED Documentation Not Impacted

CMS also proposes leaving ED codes alone:

"We are not proposing any changes to the emergency department E/M code set or to the E/M code sets for settings of care other than office-based and outpatient settings at this time. However, we are seeking public comment on whether we should make any changes to it in future years, whether by way of documentation, coding, and/or payment and, if so, what the changes should be."

Teaching Physician Documentation

In an effort to reduce the physician documentation burden, CMS proposes eliminating duplicative documentation requirements for teaching physicians (TPs) when the required information has already been documented by someone else. CMS specifically proposes the following:

"The medical records must document the extent of the teaching physician's participation in the review and direction of services furnished to each beneficiary, and that the extent of the teaching physician's participation may be demonstrated by the notes in the medical records made by a physician, resident, or nurse."

If this documentation relief is enacted, TPs would be spared from re-documenting large components of the medical record, and a TP's involvement could be recorded by another physician, resident, or nurse.

In another win for TPs, Medicare issued a regulatory update related to medical student documentation, clarifying that the TP does not have to re-document items in the medical record entered by medical students, and although the TP must perform the components of the medical service (such as a physical exam and MDM), they do not have to re-document a full note. Just a TP signature is required following the medical student's documentation:

"If the teaching physician chooses to rely on the medical student documentation and chooses not to re-document the E/M service, contractors shall consider this requirement met if the teaching physician signs and dates the medical student's entry in the medical record."

DR. GRANOVSKY is the president of LogixHealth, an ED coding and billing company, and serves as the course director of ACEP's coding and reimbursement courses. Email him questions at mgranovsky@logixhealth.com.

DOCUMENTATION SCHOOL

For more information on ED documentation issues, check out these classes at ACEP18 in October:

- **Rev Up Your Procedural and Critical Care RVUs:** Wednesday, Oct. 3, 8–8:50 a.m.
- **RVU Killers: The Most Common Reimbursement Documentation Errors:** Thursday, Oct. 4, 8–8:25 a.m.

CONTINUED FROM PAGE 1

MEET THE PRESIDENT-ELECT CANDIDATES

PLATFORM-STATEMENTS

The following members are candidates for President-Elect. They responded to this question:

What are the biggest internal and external threats to emergency medicine, and how will you address them?

Jon Mark Hirshon, MD, PhD, MPH, FACEP

Current Professional Positions: professor, department of emergency medicine and department of epidemiology and public health, University of Maryland School of Medicine, Baltimore; senior vice-chair of the University of Maryland, Baltimore Institutional Review Board

Internships and Residency: emergency medicine residency, Johns Hopkins Hospital, Johns Hopkins University, Baltimore; preventive medicine residency, Johns Hopkins Bloomberg School of Public Health

Medical Degree: MD, University of Southern California School of Medicine, Los Angeles (1990)

Response

The other night, during a busy shift, a mid-60s woman came into my ED via ambulance with hypotension and inferior changes concerning for a ST-elevation MI on the EMS-transmitted ECG. Upon arrival, we confirmed the ECG changes and activated the catheter lab, and shortly thereafter, the patient went upstairs for catheterization and stenting. The system worked—a life was saved! Unfortunately, our dysfunctional, fragmented U.S. healthcare system is under siege and threatened from many directions, both internally and externally. While the system worked today for my patient, will it work tomorrow for your patient or family member with a life-threatening emergency?

> "ACEP must, and I will, continue to fight to assure high-quality emergency care for all Americans. This is a multipronged approach, including legal, educational, and lobbying activities on both federal and state levels."
>
> *–Jon Mark Hirshon, MD, PhD, FACEP*

Assuring appropriate financial and societal support remains a critical external threat to EM. Longtime emergency physician Paul Seward recently penned an article on *Stat News* describing EDs as "the 'chewing gum and duct tape' holding together U.S. healthcare." As the cost of healthcare in the U.S. has skyrocketed, EDs are viewed as the healthcare safety net—or as stated by a previous U.S. president: "I mean, people have access to healthcare in America," he said. "After all, you just go to an ER." Out-of-pocket medical ex-

penses are mounting astronomically while insurance companies are making record profits. Many Americans are only one medical emergency away from poverty or homelessness. We, as frontline providers, see this on a daily basis. Our EDs may be our neighbors' front door to the hospital, but it is our window to the problems seen in our communities.

ACEP must, and I will, continue to fight to assure high-quality emergency care for all Americans. This is a multipronged approach, including legal, educational, and lobbying activities on both federal and state levels. Last summer, while having lunch with my senator, Ben Cardin, the federal champion of the prudent layperson standard, he was shocked to learn that prudent layperson was under siege again. ACEP and the Medical Association of Georgia are suing Anthem BlueCross BlueShield of Georgia for their policy allowing for retrospective denial for some care delivered in EDs. Previously, we sued the U.S. Department of Health and Human Services to require transparency of data and fair insurance coverage for emergency patients who are "out of network" because of a medical emergency. Our lobbying and educational efforts include almost daily interactions with policymakers and regulators, including high-quality, effective presentations at the RVS Update Committee, to assure that we are paid for the work that we do. We must, and I will, fight to make sure that we receive fair compensation for the care we deliver through supporting legal action, developing coalitions and partnerships, and testifying in front of politicians and the public.

However, assuring fair compensation is only one external threat we face. The ever-increasing regulatory burden remains a significant problem, negatively impacting our productivity and our well-being. We face this concretely on a daily basis with the growing burden of documentation as enforced by our electronic medical records. For every five minutes I spend with a patient, I spend 15 to 20 minutes documenting. This negatively impacts my rapport with patients, coworkers, and trainees. Reducing administrative burdens is critical and was a central theme of my testimony earlier this year before the House Committee on Ways and Means' Health Subcommittee on reducing administrative burdens for physicians in the Medicare program. Decreasing regulatory burdens and improving our work environment are critical aspects of improved care delivery and emergency physician well-being. This will be a critical objective of my time as ACEP President.

Internally, we are faced with the challenge of unifying the multiple voices in EM into a strong and effective chorus. We are a diverse group and bring many different perspectives together in order to care for our varied patients. Companies with greater diversity have been shown to be more successful from a business perspective. ACEP will be more successful through embracing diversity, and not just gender and race diversity but the many aspects of our practices—gender, race, ethnicity, large groups, small groups, academics, rural providers, young physicians, individuals near retirement, etc. Together, we can agree on specific topics and issues and work together collaboratively on these. This will strengthen our voice. On other topics, we can continue to disagree respectfully and professionally without personal attacks. Speaking with one voice will allow us to be heard above the discordant clamor found in Washington, D.C., and in many state capitols.

Emergency physicians are caring, thoughtful professionals. We work hard, and we play hard. We care about our patients and for our colleagues. ACEP and EM play a critical and ever-increasing role within the healthcare system. I will work together with our many partners to forcefully advocate for EM and to sustain and to grow the support for our important work. Working together, we can and will make a difference.

William Jaquis, MD, FACEP

Current Professional Positions: senior vice president, Alliance Operating Unit–Envision, East Florida Division; attending physician, Aventura Hospital, Aventura, Florida

Internships and Residency: emergency medicine residency, Case Western–Mt. Sinai Hospital, Cleveland

Medical Degree: MD, Medical College of Ohio, Toledo (1989)

Response

✔ Externally, the biggest threat is our current form of funding and paying for healthcare. The "system" is far from a coordinated entity but more a collection of stakeholders with their own interests exceeding the needs of the system as a whole. Those who fund and pay for the care are often deeply separated from the consumers of care, and the complicated approach to payments leaves us all confused. Consumers should have more transparency about what the cost to them for their care will be, but we are unable to give it to them because we have no idea across our delivery system how we will be paid, if at all. We have insurers who have hidden lists for which they will retrospectively deny payment, and every day it seems there is a new story or "study" that highlights "excessive" ED costs. In this setting, it is incredibly difficult to provide timely care for patients, help them understand the costs of that care to them, and appropriately staff and reimburse our providers. EM is unique in this battle from our EMTALA mandate to see all patients regardless of ability (or intent) to pay. Addressing this issue will take all of us acting in many different venues. For our patients, we need to continue to advocate for access by requiring essential health services to be covered and paid according to prudent layperson laws. This also has and may continue to require legal action such as the current suit (July) against Anthem. We have some solutions that are improvements to the issue of fair coverage, and that message needs to continue through coalitions, the courts, social media, and public relations.

> "We have insurers who have hidden lists for which they will retrospectively deny payment, and every day it seems there is a new story or 'study' that highlights 'excessive' ED costs. In this setting, it is incredibly difficult to provide timely care for patients, help them understand the costs of that care to them, and appropriately staff and reimburse our providers."
>
> ***–William Jaquis, MD, FACEP***

Internally, our biggest threat is our inability in many situations to find a shared vision as a physician community. As the phrase goes, we have met the enemy and he is us. I cannot determine how many meetings I have attended where the physicians spent a great deal of time arguing with each other while the non-physician team stands by, leading to no directed action. Through many means in society as a whole, we are becoming more polarized rather than recognizing what is shared in the middle. This is true of EM at times as well. Do not misunderstand: I highly value the discourse of opposing views, as they often lead me and us to a better understanding of an issue. We must, however, make sure that, in doing so, we do so with respect, and we understand there must be a forward direction. We can do so by continuing the dialogue on our important issues with civility, keeping our criticisms more private, and moving forward publicly with a shared vision and praise.

We are well positioned to address the threats and the opportunities to EM. The leadership of the College—both physician and ACEP staff—is strong and well-informed. The working relationships with Committees and Sections and Task Forces are constructive, utilizing the immense talent we have within the College. The Council leadership and the members of the Council have consistently shown their dedication to defining the important work we do. Our leaders have influence not only in the College but within their groups, within other specialty societies, and with leaders in the health systems. At the turn of our 50th year, we should recognize the tremendous growth and influence we have had not only in EM but in the entire healthcare system at a national level. Honoring that growth, we also remain vigilant, building our practice and our leaders for the next 50 years. ⊕

THE ELIQUIS STARTER PACK
Designed to support DVT/PE treatment initiation

Not actual size.

IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.
  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Eliquis®
(apixaban) tablets

THE ELIQUIS STARTER PACK OFFERS YOUR PATIENTS:

- Their first **30-day supply** of ELIQUIS treatment complete with daily dosing instructions
- **2 separate wallets** per box
  - **Wallet 1** contains ELIQUIS treatment for days 1-14 along with directions on how to step down dosing after week 1
  - **Wallet 2** contains ELIQUIS treatment for days 15-30

DVT=deep vein thrombosis; PE=pulmonary embolism.

WARNINGS AND PRECAUTIONS (cont'd)

Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.

- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

- There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

- **Refill reminder:** prompts DVT/PE patients to refill their ELIQUIS prescription

No cost to eligible patients when using the ELIQUIS **Free Trial Offer***

For more information, speak to your ELIQUIS Sales Representative or visit hcp.eliquis.com

*Eligibility Requirements and Terms of Use apply.

INDICATIONS

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

Please see Brief Summary of Full Prescribing Information, including **Boxed WARNINGS**, on the following pages.

432US1801802-02-01 08/18

Bristol-Myers Squibb Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery— ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding *[see Warnings and Precautions]*. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of apixaban is available. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS (apixaban) have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions]*
- Bleeding *[see Warnings and Precautions]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).
† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.
‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.
§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14.
¶ GI bleed includes upper GI, lower GI, and rectal bleeding.
** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

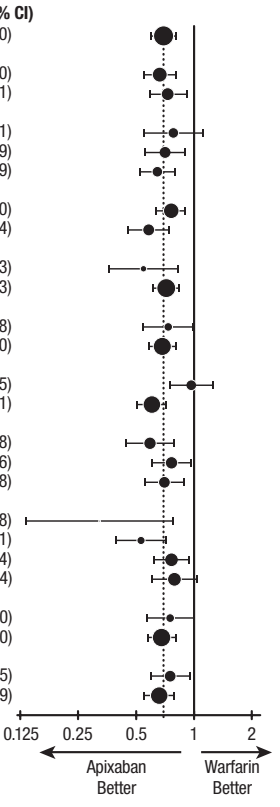
Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.
† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post-surgery).
§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
¶ CRNM = clinically relevant nonmajor.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma and catheter-site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.8% per year with apixaban versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with apixaban versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS (apixaban) therapy, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1) in full Prescribing Information]*:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1) in full Prescribing Information]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1) in full Prescribing Information]*. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2) in full Prescribing Information]*.

OVERDOSAGE

Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of apixaban is available.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in full Prescribing Information]*.

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and
Pfizer Inc
New York, New York 10017 USA

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Your Overdose Patient Doesn't Want to Quit—Now What?

Strategies for keeping patients alive until they're ready for recovery

by **EVAN SCHWARZ, MD, FACEP, FACMT; AND R. COREY WALLER, MD, MS, FACEP, DFASAM**

Editor's Note: This is the fifth part of an ongoing series on what emergency physicians can do to combat the opioid epidemic.

Ideally, every patient would want to stop using drugs. Of course, if it were that easy, we wouldn't be in the mess we are in now. Opioid addiction is much more complicated than that; changes in the frontal cortex and the hour-to-hour search for more dopamine to just feel normal lead to poor decisions and continued use.

So what do you do if your patient isn't ready to go to treatment?

Harm Reduction

Opioid overdose treatment falls under the approach of harm reduction, or the idea that we should try our best to keep this population safe until they are ready to accept help. Put simply, they can't get help if they are dead.

Critics will argue these practices just enable addicts, but the experts dispute that line of thinking. People with substance-use disorders will use drugs whether you do things to make it safer for them or not. Safety is not something that factors into their decision tree prior to using drugs. In fact, not only do harm-reduction strategies save lives, decrease HIV and hepatitis transmission, and reduce needle sticks to first responders, they do not appear to increase drug use.[1–4]

Over the past few years, increased naloxone distribution has gained the most attention as a form of harm reduction. Community distribution of naloxone appears to be successful.[5] It's been demonstrated that first responders and lay providers can learn to recognize the signs of an opioid overdose and safely administer naloxone. The data demonstrate a significant number of individuals surviving who otherwise might have died.[6]

Additionally, emergency departments are dispensing more and more naloxone. In some places, state grants have helped purchase the medication because it is unfortunately ridiculously expensive (which is a completely different conversation). In many places, Medicaid and private insurance will pay for it. Some states even allow over-the-counter access. The website PrescribeToPrevent.org is a great source to see if there are laws in your state allowing for increased naloxone distribution and Good Samaritan protection for prescribers and laypersons who may administer the drug.

Needle exchanges have been around since the late 1980s and early 1990s and have also decreased infectious disease transmission without increasing drug use. A report funded by the National Institute on Drug Abuse demonstrated a 70 percent decrease in new HIV cases due to injection drug use in Washington, D.C.[2] A review of programs in both North America and Europe demonstrated a 56 percent reduction in hepatitis C and a 74 percent reduction in transmission when combined with medication-assisted therapy.[7]

The Substance Abuse and Mental Health Services Administration (SAMHSA) also supports these programs; not only does it give out needles, it also encourages patients to seek treatment. Programs have been successfully started in many states, including West Virginia, Kentucky, and North Carolina.[8]

Although not everyone is ready to accept these concepts, many are starting to open their eyes to their value. After what can only be described as a devastating rise in newly diagnosed cases of HIV in Indiana due to oxymorphone and heroin, clean needle exchanges were introduced in 2015, which helped reduce new hepatitis C cases in one county by 50 percent.[9] However, even with that impact, county officials did not vote to reapprove the program this year. In Missouri, needle exchange legislation passed the state's House of Representatives this year, and we hope it will pass the Senate next year.

PHOTO: CDC/ DEBORA CARTAGENAP

Safe Injection

But what else can you do in the emergency department for patients who aren't ready to quit? Well, you can start by having a short discussion about drug use and safe injection practices. You can discuss how to properly clean the skin with alcohol swabs and use clean water. Drug users will commonly use a filter such as cotton, but it may be dirty or have blood products on it, which can lead to infectious complications. The benefit, in addition to decreased transmission of hepatitis C and HIV, should include fewer admissions for soft tissue infections and endocarditis.

If it is possible and doesn't place someone else at risk, patients shouldn't use alone. If they overdose, no one will be available to administer naloxone or call 911. You can frame this discussion along the lines of, "We want you to quit and hope you do, but we understand you might use again."

Once again, you are not expected to condone drug use, but judgment may stand in the way of public health and individual patient safety. It's somewhat analogous to what you might tell patients with diabetes or hypertension who need to lose weight but aren't ready to change their diet.

Finally, consider safe injection facilities. US Surgeon General Jerome Adams, MD, MPH, recently spoke to emergency physicians at ACEP's Leadership & Advocacy Conference in May. Among the topics of conversation were addiction and the opioid epidemic. He discussed harm-reduction strategies, including safe injection facilities.[10] At these facilities, injection drug users can bring their own heroin, get clean needles and alcohol swabs, and safely inject. Facility providers can dispense naloxone should an overdose occur. They can also try to intervene and discuss referral to treatment with those interested.

Such facilities are operating in Europe and Canada, with data demonstrating decreases in mortality, infectious disease, and possibly crime.[11–13] Although there is rumor of an underground facility in California and discussion in states including Washington, Pennsylvania, and New York, safe injection facilities remain illegal in the United States, and of course, they remain controversial. Critics worry they condone drug use and that you never know what people are actually injecting. Keep in mind people will inject that same substance by themselves at home or elsewhere in a much less safe environment.

Health care organizations are now beginning to discuss their role in harm-reduction strategies. The American Medical Association (AMA) voted to "support the development of private facilities where people who use intravenous drugs can inject self-provided drugs under medical supervision." At the ACEP Council meeting last year, Resolution 31 was adopted: Development and Study of Supervised Injection Facilities. The resolution joins the AMA in supporting the development and study of pilot facilities in the United States.

If any of these facilities ever go operational in the United States, we'll have to see if the results are similar to those in other countries.

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EM PICS WORTH A THOUSAND WORDS

IMAGES IN EM

DR. THOMAS is an emergency medicine resident at Highland Hospital in Oakland, California.

PHOTO: BENJAMIN THOMAS

Mr. X immediately got intubated and was rushed to the operating room. His life would never be the same, and neither would mine.

Beat Back Bias

Don't let it affect how you treat your patients

by BENJAMIN THOMAS, MD

"Don't worry about them, doc—they're a frequent flier."

"Doc, they're just drug-seeking."

These phrases are much too common in our line of work and are often dangerous introductions to patients we have yet to meet. They can immediately introduce bias, and that, in turn, can lead a provider down a path detrimental to patient care. Early in my training, I learned this lesson the hard way.

As a young resident, I had a patient who was initially described to me as a "frequent flier." This patient was homeless and well-known to the senior staff members as someone who frequented the emergency department for alcohol and drug intoxication. I went to assess "Mr. X," and he was profoundly somnolent, smelled of alcohol, and simply was not engaging in any part of my exam. "He's always like this," a nurse told me.

I decided I would come back later and reevaluate him, thinking he was just drunk. The second time around, there wasn't much change. I asked the nurse to obtain a fingerstick glucose and decided I would come back again later. I continued on with the rest of my shift and forgot about him after seeing other patients during a busy shift.

Almost three and a half hours after his initial arrival, I asked the nurse to try and ambulate Mr. X. Moments later, the nurse came back to me to say he would not wake up. I rushed over to evaluate him. "Mr. X! Mr. X!" I yelled. Nothing. I opened his eyes myself, and he had an enlarged right pupil that was barely reactive. My heart sank to my stomach, and I rushed the patient over to the CT scanner myself. My eyes were fixed on the computer screen, and there it was in plain sight staring right back at me: a large acute subdural hematoma with midline shift. Mr. X immediately got intubated and was rushed to the operating room. His life would never be the same, and neither would mine.

Bias is defined as a disproportionate weight in favor of or against one thing, person, or group compared with another, usually in a way considered to be unfair. A number of biases played into this particular case. I anchored early on the fact he was a frequent flier and usually presented with alcohol intoxication. I did not consider a broader differential for his somnolence.

He was homeless, and as I reflect now on the case, I see class bias affected how urgently I initially cared for him. Current literature indicates that although many physicians, regardless of specialty, demonstrate an implicit preference for white, upper-class individuals, this bias does not appear to impact their clinical decision making but can impact the patient experience.

Since that incident, I began asking myself questions to reduce the potential bias I may inherently bring to work:

- How do I feel toward this patient?
- Is there anything else to be found?
- Is there anything that doesn't fit? Have I distorted any of the facts?
- Am I missing a potentially life-threatening process or mimic?
- Does the information support my judgment and plan?
- Have I relied on any anchors or information that is too readily available?

We all carry implicit and explicit biases. Our job as physicians is to recognize and work to put aside our biases to provide the best care for our patients. In our line of work, the stakes are too high to have bias impact our clinical interactions and the care we deliver. Take it from me—this is not a lesson you want to learn the hard way.

DR. MILNE is chief of emergency medicine and chief of staff at South Huron Hospital, Ontario, Canada. He is on the Best Evidence in Emergency Medicine faculty and is creator of the knowledge translation project the Skeptics' Guide to Emergency Medicine (www.TheSGEM.com).

IV Lidocaine for Pain in the ED

The pyramid holds the answer!

by **KEN MILNE, MD, MSC, CCFP-EM, FCFP, FRRMS**

The Case

A 49-year-old man presents to the emergency department with the chief complaint of left lumbar back pain that radiates down his leg. He had been doing yard work at home all week to get ready for a Labor Day weekend barbecue. He tried acetaminophen and ibuprofen, but it didn't touch the pain. There are no "red flags" in his history or physical examination. The last time he hurt his back, they gave him morphine in the emergency department. The morphine worked, but it made him drowsy and nauseated, and he could not drive himself home. He asks if his pain could be taken away without an opioid.

Background

There are about 2.7 million annual ED visits for low back pain in the United States. They can be frustrating for both patients and physicians. Physicians have many pharmacological agents available to treat painful conditions in the emergency department with variable success depending on the cause (nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen, opioids, muscle relaxants, and benzodiazepines).

Anesthetic agents, like lidocaine, that target sodium channels are widely used in the emergency department for topical and local anesthesia. Lidocaine is a local anesthetic agent with analgesic, anti-hyperalgesic, and anti-inflammatory properties. It has a short half-life (60 to 120 minutes) with often predictable adverse effects.

It has been suggested that IV lidocaine could be an alternative for pain control instead of opioids or NSAIDs when these other treatment modalities have been ineffective or associated with adverse effects.

IV lidocaine for the treatment of renal colic was covered in a recent "Skeptics' Guide to Emergency Medicine" column (May 2018). The bottom line from that was that the study reviewed "does not provide good evidence for using lidocaine to treat patients presenting to the emergency department with renal colic."

Clinical Question

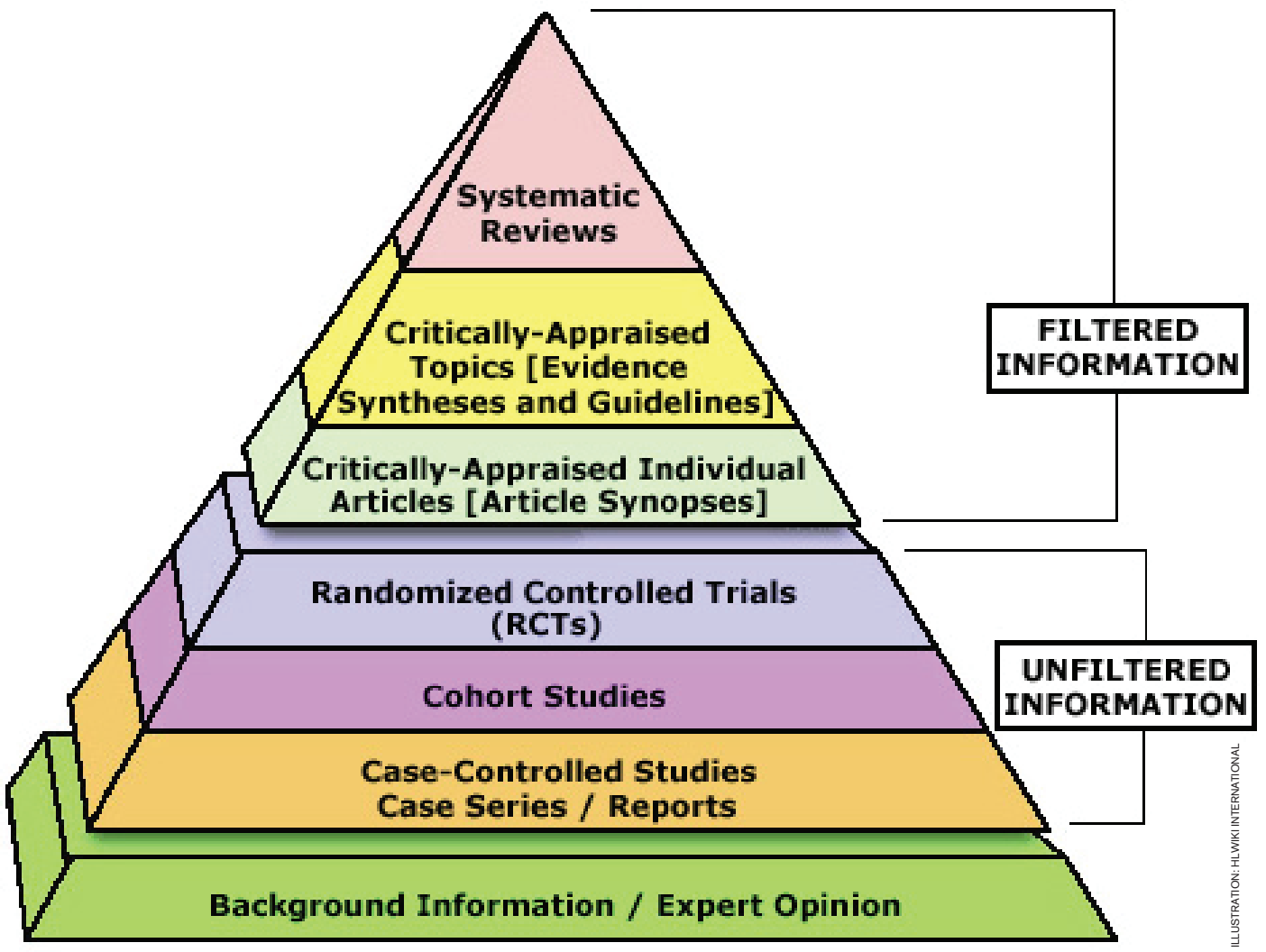
In patients presenting to the emergency department with acute or chronic pain, is the administration of IV lidocaine safe and effective?

Reference

E Silva LOJ, Scherber K, Cabrera D, et al. Safety and efficacy of intravenous lidocaine for pain management in the emergency department: a systematic review. *Ann Emerg Med.* 2018;72(2):135-144.e3.

- **Population:** Adult patients presenting to the emergency department for the management of acute or chronic pain.
  - » **Exclusions:** Studies in which patients received IV lidocaine in a setting outside the emergency department or for indications other than analgesia. Studies that used lidocaine for regional anesthesia were also not included.
- **Intervention: At least one dose of IV lidocaine given in the** emergency department.
- **Comparison: Active controls**, such as opioids and NSAIDs, or placebo controls.
- **Outcomes:**
  - » **Efficacy Outcomes:** Reduction in pain score and need for rescue analgesia.
  - » **Safety Outcomes:** Adverse drug reactions.
  - » **Risk of Bias:** Cochrane Collaboration bias appraisal tool for the randomized controlled trials (RCTs) and a modified Newcastle-Ottawa Scale tool for observational studies.
  - » **Certainty:** The certainty for each outcome was evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods.

Figure 1: Pyramid of evidence-based medicine.



Authors' Conclusions

"There is limited current evidence to define the role of intravenous lidocaine as an analgesic for patients with acute renal colic and critical limb ischemia pain in the ED. Its efficacy for other indications has not been adequately tested. The safety of lidocaine for ED pain management has not been adequately examined."

Key Results

Eight studies met inclusion/exclusion criteria, six RCTs and two case series, for a total of 536 patients. The causes of pain included radicular low back pain, renal colic, critical limb ischemia, and migraine headaches.

- **Efficacy:** There were six RCTs included and two case series for efficacy. Among the six RCTs, IV lidocaine had efficacy equivalent to that of active controls in two studies and was better than active controls in two other studies. In particular, IV lidocaine had pain score reduction comparable to or higher than that of IV morphine for pain associated with renal colic and critical limb ischemia. Lidocaine did not appear to be effective for migraine headache in two studies.
- **Safety:** There were 20 adverse events reported by six studies among 225 patients who received IV lidocaine in the emergency department, 19 non-serious events and one serious event related to an accidental overdose of lidocaine (rate 8.9 percent, 95 percent confidence interval 5.5 to 13.4 percent for any adverse event; and 0.4 percent, 95 percent confidence interval 0 to 2.5 percent for serious adverse events).

Risk of Bias

STUDY	OVERALL RISK OF BIAS
Bell et al, 1990	High
Firouzian et al, 2016	Low
Reutens et al, 1991	Unclear
Soleimanpour et al, 2012	Unclear
Tanen et al, 2014	Unclear
Vahidi et al, 2015	Low
Fitzpatrick et al, 2016	High
Soleimainpour et al, 2011	High

CONTINUED *on page 41*

...Patient seems confused...soot around mouth...

YOU SUSPECT YOUR PATIENT HAS CYANIDE POISONING.* TIME MAY BE RUNNING OUT.[1]

Suspect it? Treat with CYANOKIT.

CYANOKIT is approved for the treatment of known or suspected cyanide poisoning. If clinical suspicion of cyanide poisoning is high, administer CYANOKIT without delay.[1]

For more information, visit CYANOKIT.com.

CYANOKIT® (hydroxocobalamin for injection)

*Prior to administration of CYANOKIT, smoke inhalation victims should be assessed for exposure to fire or smoke in an enclosed area; presence of soot around the mouth, nose, or oropharynx; or altered mental status.[1]

IMPORTANT SAFETY INFORMATION

Cyanide poisoning may result from inhalation, ingestion, or dermal exposure. Prior to administration of CYANOKIT, smoke-inhalation victims should be assessed for: exposure to fire or smoke in an enclosed area; presence of soot around the mouth, nose, or oropharynx, and altered mental status. In addition to CYANOKIT, treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of any seizure activity.

Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Consideration should be given to use of alternative therapies, if available. Allergic reactions may include: anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea, and rash. Allergic reactions including angioneurotic edema have also been reported in postmarketing experience.

Acute renal failure with acute tubular necrosis, renal impairment and urine calcium oxalate crystals have been reported following CYANOKIT therapy. Monitor renal function for 7 days following CYANOKIT therapy.

Substantial increases in blood pressure may occur following CYANOKIT therapy. Elevations in blood pressure (≥180 mmHg systolic or ≥110 mmHg diastolic) were observed in approximately 18% of healthy subjects receiving hydroxocobalamin 5 g and 28% of subjects receiving 10 g.

Usage may interfere with some clinical laboratory evaluations. Also, because of its deep red color, hydroxocobalamin may cause hemodialysis machines to shut down due to an erroneous detection of a “blood leak.” This should be considered before hemodialysis is initiated in patients treated with hydroxocobalamin. Due to potential photosensitivity, patients should avoid direct sun until erythema resolves.

There are no adequate and well-controlled studies of CYANOKIT in pregnant women. CYANOKIT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Safety and effectiveness of CYANOKIT have not been established in pediatric patients.

The most common adverse reactions (>5%) included transient chromaturia, erythema, oxalate crystals in urine, rash (predominantly acneiform), increased blood pressure, nausea, headache, decreased lymphocyte percentage, and injection site reactions.

Please see Brief Summary of Prescribing Information on adjacent pages.

You are encouraged to report negative side effects of prescription drugs to the US Food and Drug Administration (FDA). Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Reference: 1. CYANOKIT (single 5-g vial) [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; 2017.

MERIDIAN MEDICAL TECHNOLOGIES
A Pfizer Company

CYANOKIT®
(hydroxocobalamin for injection)

BRIEF SUMMARY:

Consult full Prescribing Information for complete product information

Use with Other Cyanide Antidotes
Caution should be exercised when administering other cyanide antidotes simultaneously with Cyanokit, as the safety of co-administration has not been established. If a decision is made to administer another cyanide antidote with Cyanokit, these drugs should not be administered concurrently in the same intravenous line.

Incompatibility Information
Physical incompatibility (particle formation) and chemical incompatibility were observed with the mixture of hydroxocobalamin in solution with selected drugs that are frequently used in resuscitation efforts. Hydroxocobalamin is also chemically incompatible with sodium thiosulfate and sodium nitrite and has been reported to be incompatible with ascorbic acid. Therefore, these and other drugs should not be administered simultaneously through the same intravenous line as hydroxocobalamin.

Simultaneous administration of hydroxocobalamin and blood products (whole blood, packed red cells, platelet concentrate and/or fresh frozen plasma) through the same intravenous line is not recommended. However, blood products and hydroxocobalamin can be administered simultaneously using separate intravenous lines (preferably on contralateral extremities, if peripheral lines are being used).

WARNINGS AND PRECAUTIONS
Emergency Patient Management
In addition to Cyanokit, treatment of cyanide poisoning must include immediate attention to airway patency, adequacy of oxygenation and hydration, cardiovascular support, and management of any seizure activity. Consideration should be given to decontamination measures based on the route of exposure.

Allergic Reactions
Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin. Consideration should be given to use of alternative therapies, if available.

Allergic reactions may include: anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea, and rash.

Allergic reactions including angioneurotic edema have also been reported in postmarketing experience.

Renal Disorders
Cases of acute renal failure with acute tubular necrosis, renal impairment and urine calcium oxalate crystals have been reported. In some situations, hemodialysis was required to achieve recovery. Regular monitoring of renal function, including but not limited to blood urea nitrogen (BUN) and serum creatinine, should be performed for 7 days following Cyanokit therapy.

Blood Pressure Increase

Many patients with cyanide poisoning will be hypotensive; however, elevations in blood pressure have also been observed in known or suspected cyanide poisoning victims.

Elevations in blood pressure (180 mmHg or greater systolic or 110 mmHg or greater diastolic) were observed in approximately 18% of healthy subjects (not exposed to cyanide) receiving hydroxocobalamin 5 g and 28% of subjects receiving 10 g. Increases in blood pressure were noted shortly after the infusions were started; the maximal increase in blood pressure was observed toward the end of the infusion. These elevations were generally transient and returned to baseline levels within 4 hours of dosing.

Use of Blood Cyanide Assay
While determination of blood cyanide concentration is not required for management of cyanide poisoning and should not delay treatment with Cyanokit, collecting a pretreatment blood sample may be useful for documenting cyanide poisoning as sampling post-Cyanokit use may be inaccurate.

Interference with Clinical Laboratory Evaluations and Clinical Methods
Clinical Laboratory Evaluations
Because of its deep red color, hydroxocobalamin has been found to interfere with colorimetric determination of certain laboratory parameters (e.g., clinical chemistry, hematology, coagulation, and urine parameters). *In-vitro* tests indicated that the extent and duration of the interference are dependent on numerous factors such as the dose of hydroxocobalamin, analyte, methodology, analyzer, hydroxocobalamin concentration, and partially on the time between sampling and measurement.

Based on *in-vitro* studies and pharmacokinetic data obtained in healthy volunteers, the following table (Table 2) describes laboratory interference that may be observed following a 5 g dose of hydroxocobalamin. Interference following a 10 g dose can be expected to last up to an additional 24 hours. The extent and duration of interference in cyanide-poisoned patients may differ. Results may vary substantially from one analyzer to another; therefore, caution should be used when reporting and interpreting laboratory results.

Table 2: Laboratory Interference Observed with *In-Vitro* Samples of Hydroxocobalamin

LABORATORY PARAMETER			
Clinical Chemistry	**Hematology**	**Coagulation**	**Urinalysis**
No Interference Observed			
Calcium Sodium Potassium Chloride Urea GGT	Erythrocytes Hematocrit MCV Leukocytes Lymphocytes Monocytes Eosinophils Neutrophils Platelets		
Artificially Increased*			
Creatinine Bilirubin Triglycerides Cholesterol Total protein Glucose Albumin Alkaline phosphatase	Hemoglobin MCH MCHC Basophils		pH (with all doses) Glucose Protein Erythrocytes Leukocytes Ketones Bilirubin Urobilinogen Nitrite
Artificially Decreased*			
ALT Amylase			pH (with equivalent doses of <5 g)
Unpredictable			
Phosphate Uric Acid AST CK CKMB LDH		aPTT PT (Quick or INR)	
Duration of Interference			
24 hours with the exception of bilirubin (up to 4 days)	12-16 hours	24-48 hours	48 hours up to 8 days; color changes may persist up to 28 days

*10% or greater interference observed on at least 1 analyzer

Analyzers used: ACL Futura (Instrumentation Laboratory), AxSYM®/Architect™ (Abbott), BM Coasys[110] (Boehringer Mannheim), CellDyn 3700® (Abbott), Clinitek® 500 (Bayer), Cobas Integra® 700, 400 (Roche), Gen-S Coultronics, Hitachi 917, STA® Compact, Vitros® 950 (Ortho Diagnostics)

Clinical Methods
Because of its deep red color, hydroxocobalamin may cause hemodialysis machines to shut down due to an erroneous detection of a “blood leak.” This should be considered before hemodialysis is initiated in patients treated with hydroxocobalamin.

Photosensitivity
Hydroxocobalamin absorbs visible light in the UV spectrum. It therefore has potential to cause photosensitivity. While it is not known if the skin redness predisposes to photosensitivity, patients should be advised to avoid direct sun while their skin remains discolored.

ADVERSE REACTIONS
Serious adverse reactions with hydroxocobalamin include allergic reactions, renal disorders and increases in blood pressure.

Clinical Studies Experience
Because clinical trials were conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice.

Experience in Healthy Subjects
A double-blind, randomized, placebo-controlled, single-ascending-dose (2.5, 5, 7.5, and 10 g) study was conducted to assess the safety, tolerability, and pharmacokinetics of hydroxocobalamin in 136 healthy adult subjects. Because of the dark red color of hydroxocobalamin, the two most frequently occurring adverse reactions were chromaturia (red-colored urine) which was reported in all subjects receiving a 5 g dose or greater; and erythema (skin redness), which occurred in most subjects receiving a 5 g dose or greater. Adverse reactions reported in at least 5% of the 5 g dose group and corresponding rates in the 10 g and placebo groups are shown in Table 3.

Table 3: Incidence of Adverse Reactions Occurring in >5% of Subjects in 5 g Dose Group and Corresponding Incidence in 10 g Dose Group and Placebo

	5 g Dose Group		**10 g Dose Group**	
ADR	**Hydroxocobalamin N=66 n (%)**	**Placebo N=22 n (%)**	**Hydroxocobalamin N=18 n (%)**	**Placebo N=6 n (%)**
Chromaturia (red colored urine)	66 (100)	0	18 (100)	0
Erythema	62 (94)	0	18 (100)	0
Oxalate crystals in urine	40 (61)	1 (4)	10 (56)	0
Rash*	13 (20)	0	8 (44)	0
Blood pressure increased	12 (18)	0	5 (28)	0
Nausea	4 (6)	1 (5)	2 (11)	0
Headache	4 (6)	1 (5)	6 (33)	0
Lymphocyte percent decreased	5 (8)	0	3 (17)	0
Infusion site reaction	4 (6)	0	7 (39)	0

*Rashes were predominantly acneiform

In this study, the following adverse reactions were reported to have occurred in a dose-dependent fashion and with greater frequency than observed in placebo-treated cohorts: increased blood pressure (particularly diastolic blood pressure), rash, nausea, headache and infusion site reactions. All were mild to moderate in severity and resolved spontaneously when the infusion was terminated or with standard supportive therapies.

Other adverse reactions reported in this study and considered clinically relevant were:

- *Eye disorders:* swelling, irritation, redness
- *Gastrointestinal disorders:* dysphagia, abdominal discomfort, vomiting, diarrhea, dyspepsia, hematochezia
- *General disorders and administration site conditions:* peripheral edema, chest discomfort
- *Immune system disorders:* allergic reaction
- *Nervous system disorders:* memory impairment, dizziness
- *Psychiatric disorders:* restlessness
- *Respiratory, thoracic and mediastinal disorders:* dyspnea, throat tightness, dry throat
- *Skin and subcutaneous tissue disorders:* urticaria, pruritus
- *Vascular disorders:* hot flush

Experience in Known or Suspected Cyanide Poisoning Victims

Four open-label, uncontrolled, clinical studies (one of which was prospective and three of which were retrospective) were conducted in known or suspected cyanide-poisoning victims. A total of 245 patients received hydroxocobalamin treatment in these studies. Systematic collection of adverse events was not done in all of these studies and interpretation of causality is limited due to the lack of a control group and due to circumstances of administration (e.g., use in fire victims). Adverse reactions reported in these studies listed by system organ class included:

- *Cardiac disorders:* ventricular extrasystoles
- *Investigations:* electrocardiogram repolarization abnormality, heart rate increased
- *Respiratory, thoracic, and mediastinal disorders:* pleural effusion

Adverse reactions common to both the studies in known or suspected cyanide poisoning victims and the study in healthy volunteers are listed in the healthy volunteer section only and are not duplicated in this list.

Postapproval Experience

The following adverse reactions have been identified during postapproval use of Cyanokit. Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Cases of acute renal failure with acute tubular necrosis, renal impairment and urine calcium oxalate crystals have been reported in patients treated with Cyanokit.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with Cyanokit.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no adequate and well controlled studies of Cyanokit in pregnant women. In animal studies, hydroxocobalamin caused skeletal and visceral (soft tissue) abnormalities at exposures (based on AUC) similar to human exposures at the therapeutic dose. Cyanokit should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because cyanide readily crosses the placenta, maternal cyanide poisoning results in fetal cyanide poisoning. Timely treatment of the pregnant mother may be lifesaving for both mother and fetus.

In animal studies, pregnant rats and rabbits received Cyanokit (75, 150, or 300 mg/kg/d) during the period of organogenesis. Following intraperitoneal dosing in rats and intravenous dosing in rabbits, maternal exposures were equivalent to 0.5, 1, or 2 times the human exposure at the therapeutic dose (based on AUC). In the high dose groups for both species, maternal toxicity occurred, and there was a reduced number of live fetuses due to embryofetal resorptions. In addition, decreased live fetal weight occurred in high dose rats, but not in rabbits. Incomplete skeletal ossification occurred in both rats and rabbits. In rats, two fetuses of the high dose group and two fetuses of the mid dose group (each from a different litter) had short, rudimentary or small front or hind legs. Rabbit litters and fetuses exhibited a dose dependent increase in various gross soft tissue and skeletal anomalies. The main findings in rabbits were flexed, rigid flexor or medially rotated forelimbs or hindlimbs and domed heads at external examination; enlarged anterior or posterior fontanelles of the ventricles of the brain and flat, bowed or large ribs at skeletal examination; and dilated ventricles of the brain, and thick wall of the stomach at visceral examination.

Labor and Delivery

The effect of Cyanokit on labor and delivery is unknown.

Nursing Mothers

It is not known whether hydroxocobalamin is excreted in human milk. Cyanokit may be administered in life-threatening situations, and therefore, breast-feeding is not a contraindication to its use. Because of the unknown potential for adverse reactions in nursing infants, the patient should discontinue nursing after receiving Cyanokit.

Pediatric Use

Safety and effectiveness of Cyanokit have not been established in this population. In non-US marketing experience, a dose of 70 mg/kg has been used to treat pediatric patients.

Geriatric Use

Approximately 50 known or suspected cyanide poisoning victims aged 65 or older received hydroxocobalamin in clinical studies. In general, the safety and effectiveness of hydroxocobalamin in these patients was similar to that of younger patients. No adjustment of dose is required in elderly patients.

Renal Impairment

The safety and effectiveness of Cyanokit have not been studied in patients with renal impairment. Hydroxocobalamin and cyanocobalamin are eliminated unchanged by the kidneys.

Hepatic Impairment

The safety and effectiveness of Cyanokit have not been studied in patients with hepatic impairment.

OVERDOSAGE

No data are available about overdose with Cyanokit in adults. Should overdose occur, treatment should be directed to the management of symptoms. Hemodialysis may be effective in such a circumstance, but is only indicated in the event of significant hydroxocobalamin-related toxicity. Because of its deep red color, hydroxocobalamin may interfere with the performance of hemodialysis machines.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of hydroxocobalamin. Hydroxocobalamin was negative in the following mutagenicity assays: *in-vitro* bacterial reverse mutation assay using *Salmonella typhimurium* and *Escherichia coli* strains, an *in-vitro* assay of the tk locus in mouse lymphoma cells, and an *in-vivo* rat micronucleus assay.

The effect of hydroxocobalamin on fertility has not been evaluated.

PATIENT COUNSELING INFORMATION

Cyanokit is indicated for cyanide poisoning and in this setting, patients will likely be unresponsive or may have difficulty in comprehending counseling information.

Erythema and Chromaturia

Patients should be advised that skin redness may last up to 2 weeks and urine coloration may last for up to 5 weeks after administration of Cyanokit. While it is not known if the skin redness predisposes to photosensitivity, patients should be advised to avoid direct sun while their skin remains discolored.

Rash

In some patients, an acneiform rash may appear anywhere from 7 to 28 days following hydroxocobalamin treatment. This rash will usually resolve without treatment within a few weeks.

Renal Disorders

Patients should be advised that renal function will be monitored for 7 days following treatment with Cyanokit or, in the event of renal impairment, until renal function returns to normal.

Pregnancy and Breast-feeding

Patients should be advised that maternal cyanide poisoning results in fetal cyanide poisoning. Treatment for cyanide poisoning may be lifesaving for both mother and fetus. Patients should notify their physician if they were pregnant during therapy with Cyanokit. It is not known whether hydroxocobalamin is excreted in human milk.

This brief summary is based on CYANOKIT® (hydroxocobalamin for injection) Prescribing Information Version 180_US_20171_NO, Issued: June 2017. For current package insert and further product information, please visit www.cyanokit.com or call Pfizer Medical Information toll-free at 1-800-438-1985.

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'X-ray Normal' Is Not a Diagnosis

Tips for diagnosing occult fractures in the emergency department

by ARUN SAYAL, MD, CCFP(EM)

Written from the perspective of an emergency physician who also runs a weekly minor fracture clinic, this column is intended to highlight a few key ED teaching points for commonly missed and commonly mismanaged ED orthopedic cases.

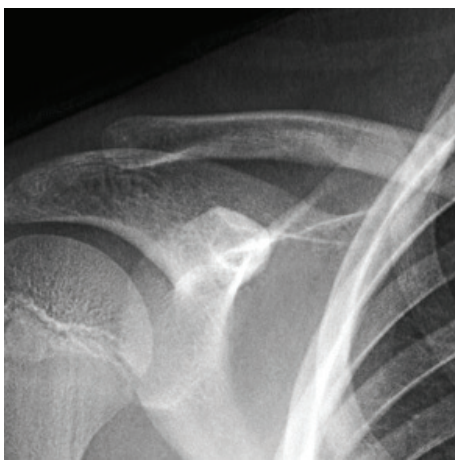
Most ED patients with a negative knee X-ray will have a soft tissue injury (STI). However, scattered among those STIs are many commonly missed diagnoses. There can be an operative STI (eg, a quadriceps or patellar tendon rupture), a septic knee, a limb-threatening spontaneously reduced knee dislocation (rarely), or an occult fracture. In this article, we focus on diagnostic strategies for occult fractures in the ED.

From a diagnostic point of view, we must appreciate that while X-rays are good tests, they are not perfect. It is well-recognized that 20 to 30 percent of scaphoid fractures are radiographically occult.[1,2] For fractures around the knee, the sensitivity of knee X-rays is around 85 percent.[3,4] Though not specifically studied, the sensitivity of plain radiographs for detecting fractures in ED patients with musculoskeletal injuries is estimated at 90 to 95 percent.

Here are four cases from our hospital. All four patients had an occult fracture.

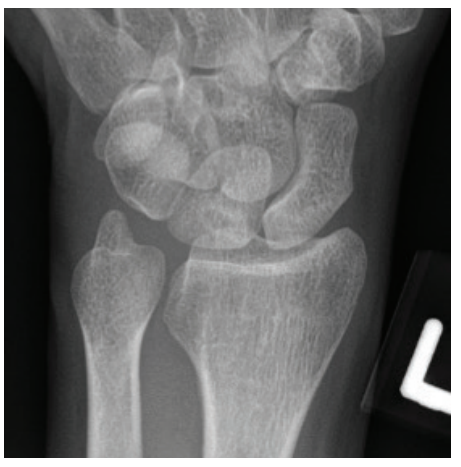
CASE 1

A 12-year-old boy fell on his shoulder. The physical exam showed a tender, swollen midclavicle. X-rays were negative, and he was diagnosed with an STI of the clavicle. Treatment: a sling and follow-up in the minor fracture clinic.



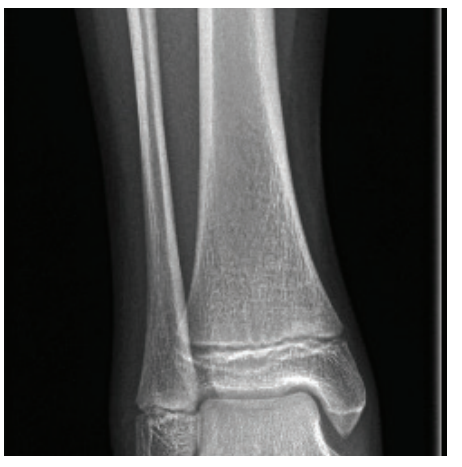
CASE 2

A 13-year-old girl twisted her ankle. Her physical exam showed an antalgic gait and a sore and swollen ankle. X-rays were negative. She was diagnosed with a Salter-Harris I distal fibula versus an ankle sprain. Treatment: a splint and follow-up in the minor fracture clinic.



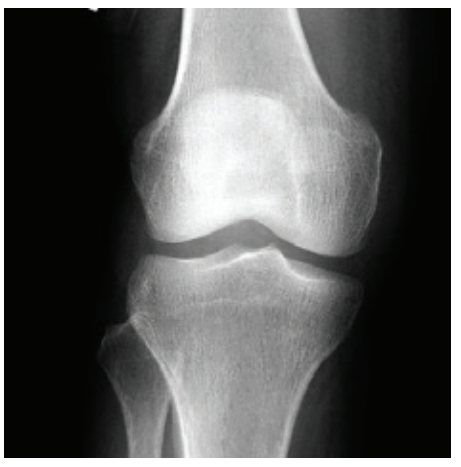
CASE 3

A 69-year-old woman fell on her outstretched hand. Her physical exam revealed a tender, swollen distal radius. X-rays were negative, and she was diagnosed with a probable STI wrist. Treatment: a splint and follow-up in the minor fracture clinic.



CASE 4

A 72-year-old woman twisted her knee. Her physical exam revealed an antalgic gait and a tender, swollen knee. X-rays were negative, and she was diagnosed with a medial collateral ligament injury. Treatment: A splint and follow-up in the minor fracture clinic.



PHOTOS: ARUN SAYAL

Fracture Risk

In the emergency department, X-rays are often used as diagnostic tools, but it's better to think of X-rays as fracture management tools. In simple terms, a fracture can occur in one of two ways. Fractures can occur via abnormal force on normal bone. For example, a 25-year-old man falls off a roof and suffers a comminuted fracture of his distal radius.

Alternatively, fractures can occur via normal force on abnormal bone. For example, an 85-year-old man with osteoporosis falls from a standing height and suffers a comminuted fracture of his distal radius. Elderly patients commonly fracture their hip without falling, secondary to a relatively minor rotational force applied to a long bone with osteoporosis.

So those with weaker bone (i.e., the elderly and young) have a heightened awareness for fracture and therefore require greater skepticism for a normal X-ray.

Better detection of occult fractures starts with appreciating that, for some reason, many clinicians have a different, perhaps flawed diagnostic approach to musculoskeletal patients. When a normal radiograph is available prior to exam, our index of suspicion declines, but it shouldn't be zero. Don't be biased by a normal radiograph. Shortchanging a patient's history and physical exam opens the door to missing subtle presentations.

To diagnose a patient with a fracture, do your best to determine:

1. The mechanism of injury, including both the magnitude and direction of force—these factors predict injury patterns.
2. The events after the injury. Delayed pain is less likely to be a fracture.
3. Age, previous injuries, past medical history, and medications. Younger patients have softer/weaker bone; older patients have osteoporosis; orthopedic implants give rise to subtle periprosthetic fractures; neuropathy diminishes pain; long-term steroids can cause osteoporosis, etc.
4. Signs of fracture, such as swelling, focal tenderness, and decreased range of motion. We must confirm what we suspect by history through examination.

Once you have determined a differential diagnosis for a patient and your pretest probability for a fracture, then and only then should you consider an X-ray. In fact, if the likelihood of an abnormal X-ray is low, consider not ordering the test. And if your pretest probability is high, don't dismiss a diagnosis of fracture just because the X-ray is normal.

As diagnosticians, we routinely apply Bayes' theorem. We determine a pretest probability based on history and a physical exam. Then we order and interpret the test. With those result(s), we now determine our posttest probability.

Likelihood ratios (LRs) help us understand how good a diagnostic test is.[5] An LR of 1 adds nothing to our diagnostic impression. But a high or low LR can make a diagnosis more or less probable, respectively.

The literature is not clear on a target LR for emergency department patients with a musculoskeletal injury and a negative X-ray, but a reasonable estimate is 0.05–0.1. For such patients, there is about a 90 to 95 percent chance they do not have a fracture versus a 5 to 10 percent chance they do have a fracture. So let's split the difference and use an LR of 7.5 percent (ie, 0.075).

Example Patients

Imagine that on your next shift, you see two patients with hip pain and normal X-rays. Patient A is a 25-year-old male who slipped two stairs onto his right hip. He has a limp and lateral hip tenderness, but he has a good range of motion (neither shortened or externally rotated). His estimated pretest probability for a fracture is 10 percent.

Patient B is a 78-year-old male who fell on his right hip from standing. He can't walk due to the pain, is tender to palpation laterally at the hip, and has quite reduced active and passive range of motion of the hip due to pain (neither shortened or externally rotated). His estimated pretest probability for a fracture is 90 percent.

You mark Patient A's 10 percent pretest probability of a fracture on a Fagan nomogram on the left axis, then draw a line from that mark through the estimated LR of 0.075 on the center axis and see where it intersects on post-test probability (ie, the right axis). See the blue line on Figure 1. Given the negative X-ray, you see the post-test probability of fracture is now less than 1 percent.

You do the same for Patient B, and despite his pretest probability of 90 percent for a fracture, you see the negative X-ray has driven the post-test probability of fracture down to around 40 percent. See the red line on Figure 1.

Negative X-rays in the face of a low pretest probability are unlikely to have a fracture, of course. And we should keep the possibility of a fracture higher on the differential diagnosis for patients with a higher pretest probability for fracture and negative X-rays.

Remember this axiom: The purpose of any test is not to make the diagnosis but rather to affect our pre-test probability.

Case Resolutions

Case 1: occult mid-shaft clavicle fracture
The 12-year-old boy who fell on his shoulder: When he returned one week later he was still tender and swollen and looked like he had a clavicle fracture. He was kept in a sling, and X-rays repeated three weeks later revealed the fracture.

Case 2: occult distal tibia fracture
The 13-year-old girl with a twisted ankle: When she returned one week later, her mechanism was external rotation (a red flag, see image), and she was tender over her distal tibia. X-rays taken three weeks later showed an occult distal tibia fracture.

Case 3: occult distal radius fracture
The 69-year-old woman who fell on her outstretched hand: When she returned one week later, she was still tender and swollen and looked like she had a distal radius fracture. She was kept in a splint, and X-rays repeated at four weeks revealed the fracture.

Case 4: occult lateral tibial plateau fracture
The 72-year-old woman who twisted her knee: When she returned one week later, she was still unable to bear weight on the knee, and she was swollen and tender over the lateral joint line. Follow-up imaging revealed a lateral tibial plateau fracture.

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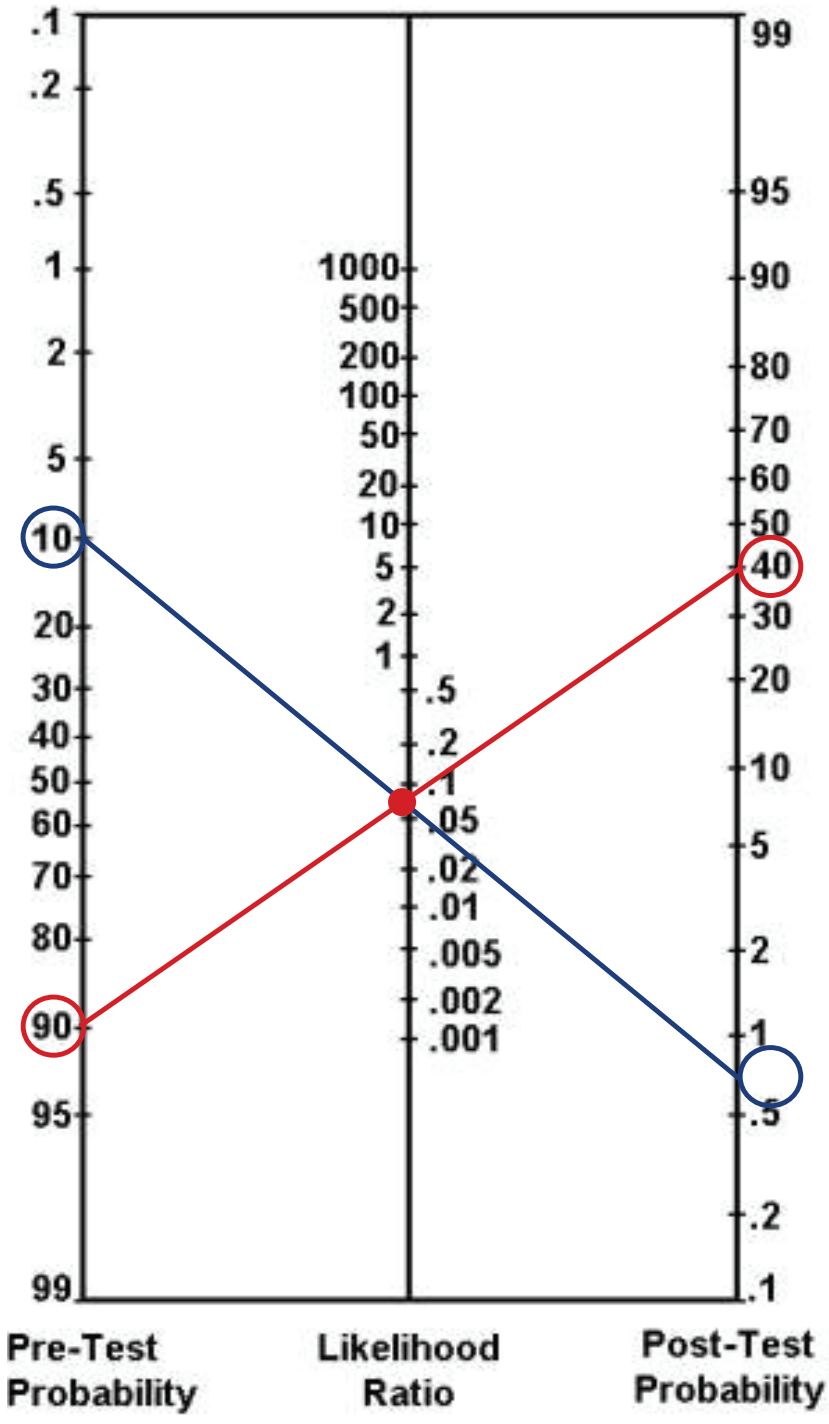
FIGURE 1

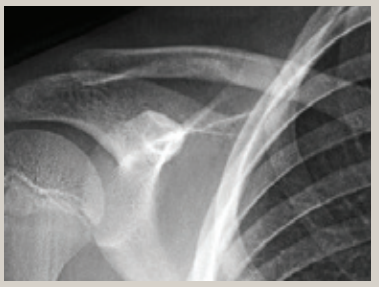


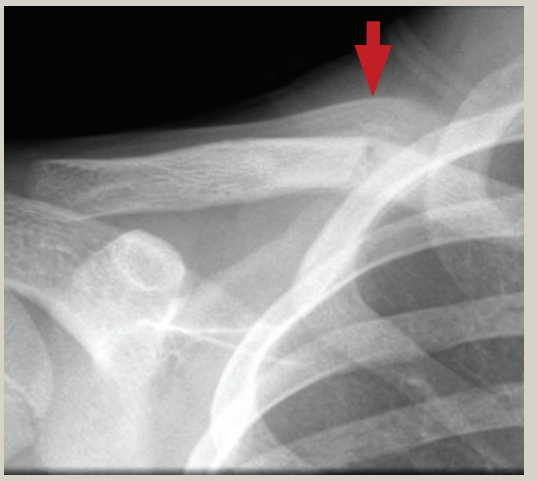
A Fagan nomogram can be used to chart the chance that a patient with a negative X-ray has a fracture. Using a likelihood ratio of 0.075 (center line), the 10 percent pretest probability (left line) of Patient A (blue line) indicates a less than 1 percent post-test probability (right line). The 90 percent pretest probability (left line) of Patient B (red line) indicates a 40 percent post-test probability (right line).

CASE 1: Occult mid-shaft clavicle fracture

BELOW: Day 1 – normal

RIGHT: Week 3 – fracture and callus

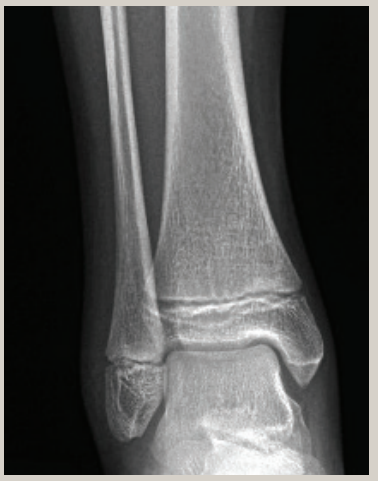


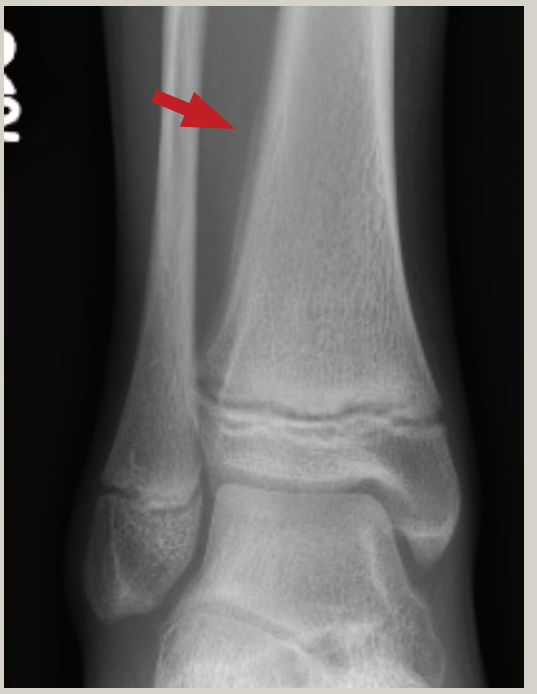


CASE 2: Occult distal tibia fracture

BELOW: Day 1 – normal

RIGHT: Week 3 – subtle periosteal reaction lateral aspect distal tibia

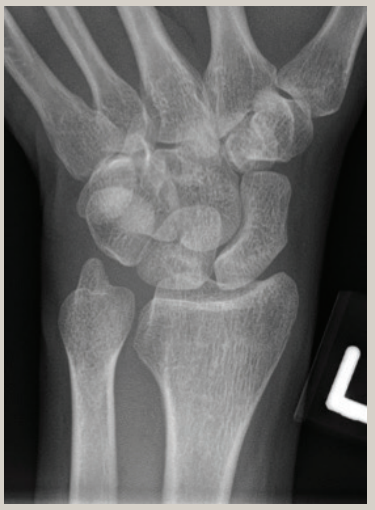


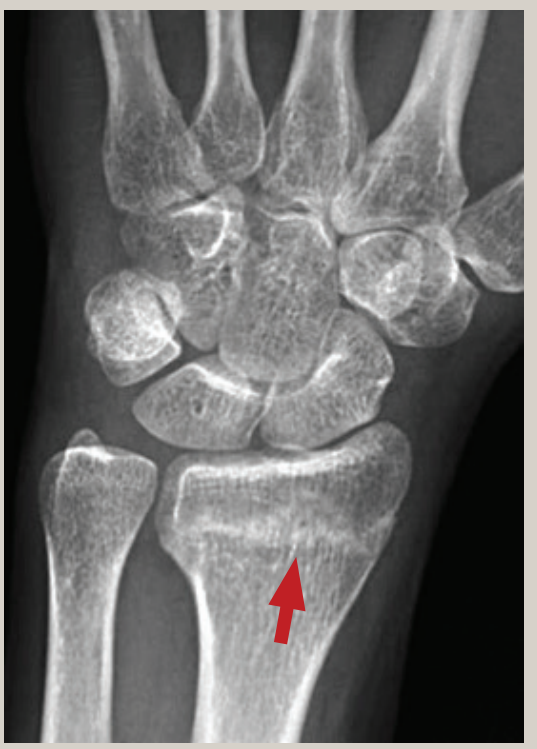


CASE 3: Occult distal radius fracture

BELOW: Day 1 – normal

RIGHT: Week 4 – sclerosis across distal radius

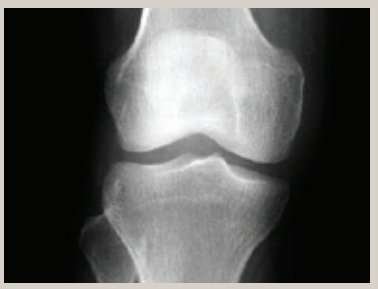


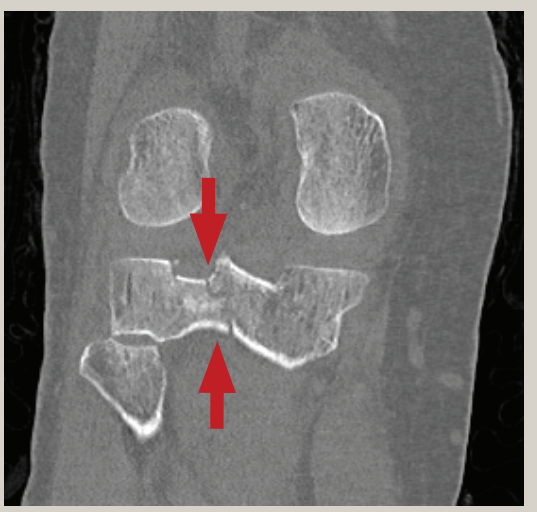


CASE 4: Occult lateral tibial plateau fracture

BELOW: Day 1 – no a fracture

RIGHT: Day 5 – CT: mildly depressed lateral tibial plateau





Xarelto®
rivaroxaban tablets

Choose the only NOAC with...

Extensive safety and efficacy data in the most patients studied with ***NVAF*** at a higher risk* of stroke[1-5]

AND

A major bleeding rate as low as aspirin with superior efficacy in recurrent ***DVT/PE*** risk reduction†[6]

†After 6 months initial treatment.

*$CHADS_2$ scores 3 to 6 in pivotal NOAC phase 3 trials: ROCKET AF (N=12,402), ARISTOTLE (N=5502), ENGAGE-AF (N=~11,200), and RE-LY (N=5882).

INDICATIONS

XARELTO® is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). There are limited data on the relative effectiveness of XARELTO® and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.

XARELTO® is indicated for the treatment of deep vein thrombosis (DVT). XARELTO® is indicated for the treatment of pulmonary embolism (PE). XARELTO® is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO® INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. Premature discontinuation of XARELTO® increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO®, increases the risk of thrombotic events. If anticoagulation with XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO® who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **Use of indwelling epidural catheters**
- **Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants, *see* Drug Interactions**
- **A history of traumatic or repeated epidural or spinal punctures**
- **A history of spinal deformity or spinal surgery**
- **Optimal timing between the administration of XARELTO® and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

DVT = deep vein thrombosis; NOAC = non-vitamin K antagonist oral anticoagulant; NVAF = nonvalvular atrial fibrillation; PE = pulmonary embolism.

Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit www.XareltoHCP.com/PI.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to XARELTO® (eg, anaphylactic reactions)

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events After Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including XARELTO®, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO® to warfarin in clinical trials in atrial fibrillation patients. If XARELTO® is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Risk of Bleeding:** XARELTO® increases the risk of bleeding and can cause serious or fatal bleeding. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO® in patients with active pathological hemorrhage.
  - A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable.
  - Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, NSAIDs, selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. To reduce the potential risk of bleeding associated with the concurrent use of XARELTO® and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO®. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO® is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (ie, 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO®. The next XARELTO® dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO® for 24 hours. Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), or bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.
- **Use in Patients With Renal Impairment:**
  - **Nonvalvular Atrial Fibrillation:** Periodically assess renal function as clinically indicated (ie, more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation of XARELTO® in patients who develop acute renal failure while on XARELTO®.
  - **Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.
  - **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** Avoid the use of XARELTO® in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO® should discontinue the treatment.
- **Use in Patients With Hepatic Impairment:** No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO® in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy, since drug exposure and bleeding risk may be increased.
- **Use With P-gp and Strong CYP3A4 Inhibitors or Inducers:** Avoid concomitant use of XARELTO® with known combined P-gp and strong CYP3A4 inhibitors. Avoid concomitant use of XARELTO® with drugs that are known combined P-gp and strong CYP3A4 inducers.
- **Risk of Pregnancy-Related Hemorrhage:** In pregnant women, XARELTO® should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO® dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO® cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (eg, a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Patients With Prosthetic Heart Valves:** The safety and efficacy of XARELTO® have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO® is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients/Patients Who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of XARELTO® is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

DRUG INTERACTIONS

- Combined P-gp and strong CYP3A4 inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding.
- Combined P-gp and strong CYP3A4 inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.
- XARELTO® should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (eg, erythromycin) unless the potential benefit justifies the potential risk.
- Coadministration of enoxaparin, warfarin, aspirin, clopidogrel, and chronic NSAID use may increase the risk of bleeding.
- Avoid concurrent use of XARELTO® with other anticoagulants due to increased bleeding risk, unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** The limited available data on XARELTO® in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO® with caution in pregnant patients because of the potential for pregnancy-related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO® cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO® for the mother and possible risks to the fetus when prescribing XARELTO® to a pregnant woman.
  - Fetal/Neonatal adverse reactions: Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.
  - Labor or delivery: The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of XARELTO® in this setting.
  - There are no adequate or well-controlled studies of XARELTO® in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage.
- **Lactation:** Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XARELTO® and any potential adverse effects on the breastfed infant from XARELTO® or from the underlying maternal condition.
- **Females and Males of Reproductive Potential:** Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.
- **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

OVERDOSAGE

- Discontinue XARELTO® and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of XARELTO® overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable.

ADVERSE REACTIONS IN CLINICAL STUDIES

- The most common adverse reactions with XARELTO® were bleeding complications.

Please see accompanying Brief Summary of full Prescribing Information, including Boxed WARNINGS, or visit www.XareltoHCP.com/PI.

References: 1. Patel MR, Mahaffey KW, Garg J, et al; and the ROCKET AF Steering Committee, for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. **2.** Granger CB, Alexander JH, McMurray JJV, et al; for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. **3.** Connolly SJ, Ezekowitz MD, Yusuf S, et al; and the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. **4.** Giugliano RP, Ruff CT, Braunwald E, et al; for the ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. **5.** Savaysa® [prescribing information]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015. **6.** Weitz JI, Lensing AWA, Prins MH, et al; for the EINSTEIN CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222.

083074-171026

Xarelto® rivaroxaban tablets

Janssen Pharmaceuticals, Inc.

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Brief Summary of Prescribing Information for XARELTO® (rivaroxaban)

XARELTO® (rivaroxaban) tablets, for oral use
See package insert for full Prescribing Information

WARNING: (A) PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. Premature discontinuation of XARELTO increases the risk of thrombotic events

Premature discontinuation of any oral anticoagulant, including XARELTO, increases the risk of thrombotic events. If anticoagulation with XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.3, 2.8), in full Prescribing Information, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

B. Spinal/epidural hematoma

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of XARELTO and neuraxial procedures is not known**

***[see Warnings and Precautions and Adverse Reactions]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thrombo-prophylaxis *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation: XARELTO is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1) in full Prescribing Information]*.

Treatment of Deep Vein Thrombosis: XARELTO is indicated for the treatment of deep vein thrombosis (DVT).

Treatment of Pulmonary Embolism: XARELTO is indicated for the treatment of pulmonary embolism (PE).

Reduction in the Risk of Recurrence of Deep Vein Thrombosis and/or Pulmonary Embolism: XARELTO is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: XARELTO is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions]*
- severe hypersensitivity reaction to XARELTO (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including XARELTO, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.3, 2.8) and Clinical Studies (14.1) in full Prescribing Information]*.

Risk of Bleeding: XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue XARELTO in patients with active pathological hemorrhage. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Concomitant use of other drugs that impair hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors.

Concomitant use of drugs that are known combined P-gp and strong CYP3A4 inhibitors increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions]*.

Reversal of Anticoagulant Effect: A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

To reduce the potential risk of bleeding associated with the concurrent use of XARELTO and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of XARELTO *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of XARELTO is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

An indwelling epidural or intrathecal catheter should not be removed before at least 2 half-lives have elapsed (i.e., 18 hours in young patients aged 20 to 45 years and 26 hours in elderly patients aged 60 to 76 years), after the last administration of XARELTO *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. The next XARELTO dose should not be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of XARELTO for 24 hours.

Should the physician decide to administer anticoagulation in the context of epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently to detect any signs or symptoms of neurological impairment, such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs or symptoms. If signs or symptoms of spinal hematoma are suspected, initiate urgent diagnosis and treatment including consideration for spinal cord decompression even though such treatment may not prevent or reverse neurological sequelae.

Use in Patients with Renal Impairment: Nonvalvular Atrial Fibrillation: Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly *[see Dosage and Administration (2.4) in full Prescribing Information]*. Consider dose adjustment or discontinuation of XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations]*.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population *[see Use in Specific Populations]*.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations]*.

Use in Patients with Hepatic Impairment: No clinical data are available for patients with severe hepatic impairment.

Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy since drug exposure and bleeding risk may be increased *[see Use in Specific Populations]*.

Use with P-gp and Strong CYP3A4 Inhibitors or Inducers: Avoid concomitant use of XARELTO with known combined P-gp and strong CYP3A4 inhibitors *[see Drug Interactions]*.

Avoid concomitant use of XARELTO with drugs that are known combined P-gp and strong CYP3A4 inducers *[see Drug Interactions]*.

Risk of Pregnancy-Related Hemorrhage: In pregnant women, XARELTO should be used only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

Patients with Prosthetic Heart Valves: The safety and efficacy of XARELTO have not been studied in patients with prosthetic heart valves. Therefore, use of XARELTO is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients Who Require Thrombolysis or Pulmonary Embolectomy: Initiation of XARELTO is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

ADVERSE REACTIONS

The following adverse reactions are also discussed in other sections of the labeling:

- Increased risk of stroke after discontinuation in nonvalvular atrial fibrillation *[see Boxed Warning and Warnings and Precautions]*
- Bleeding risk *[see Warnings and Precautions]*
- Spinal/epidural hematoma *[see Boxed Warning and Warnings and Precautions]*

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 18560 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF); 6962 patients who received XARELTO 15 mg orally twice daily for three weeks followed by 20 mg orally once daily to treat DVT or PE (EINSTEIN DVT, EINSTEIN PE), 10 mg or 20 mg orally once daily (EINSTEIN Extension, EINSTEIN CHOICE) to reduce the risk of recurrence of DVT and/or PE; and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

Hemorrhage: The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF trial.

Table 1: Bleeding Events in ROCKET AF*- On Treatment Plus 2 Days

Parameter	XARELTO N=7111 n (%/year)	Warfarin N=7125 n (%/year)	XARELTO vs. Warfarin HR (95% CI)
Major Bleeding†	395 (3.6)	386 (3.5)	1.04 (0.90, 1.20)
Intracranial Hemorrhage (ICH)‡	55 (0.5)	84 (0.7)	0.67 (0.47, 0.93)
Hemorrhagic Stroke§	36 (0.3)	58 (0.5)	0.63 (0.42, 0.96)
Other ICH	19 (0.2)	26 (0.2)	0.74 (0.41, 1.34)
Gastrointestinal (GI)¶	221 (2.0)	140 (1.2)	1.61 (1.30, 1.99)
Fatal Bleeding#	27 (0.2)	55 (0.5)	0.50 (0.31, 0.79)
ICH	24 (0.2)	42 (0.4)	0.58 (0.35, 0.96)
Non-intracranial	3 (0.0)	13 (0.1)	0.23 (0.07, 0.82)

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

‡ Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.

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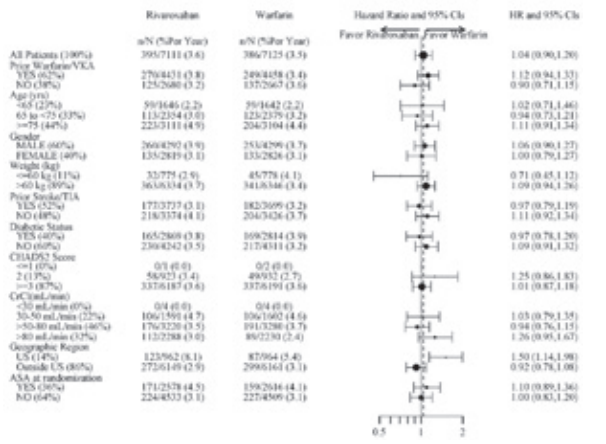
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.

Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

Figure 1 shows the risk of major bleeding events across major subgroups.

Figure 1: Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF – On Treatment Plus 2 Days



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Treatment of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE): EINSTEIN DVT and EINSTEIN PE Studies: In the pooled analysis of the EINSTEIN DVT and EINSTEIN PE clinical studies, the most frequent adverse reactions leading to permanent drug discontinuation were bleeding events, with XARELTO vs. enoxaparin/Vitamin K antagonist (VKA) incidence rates of 1.7% vs. 1.5%, respectively. The mean duration of treatment was 208 days for XARELTO-treated patients and 204 days for enoxaparin/VKA-treated patients.

Table 2 shows the number of patients experiencing major bleeding events in the pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies.

Table 2: Bleeding Events* in the Pooled Analysis of EINSTEIN DVT and EINSTEIN PE Studies

Parameter	XARELTO† N=4130 n (%)	Enoxaparin/ VKA† N=4116 n (%)
Major bleeding event	40 (1.0)	72 (1.7)
Fatal bleeding	3 (<0.1)	8 (0.2)
Intracranial	2 (<0.1)	4 (<0.1)
Non-fatal critical organ bleeding	10 (0.2)	29 (0.7)
Intracranial‡	3 (<0.1)	10 (0.2)
Retroperitoneal‡	1 (<0.1)	8 (0.2)
Intraocular‡	3 (<0.1)	2 (<0.1)
Intra-articular‡	0	4 (<0.1)
Non-fatal non-critical organ bleeding§	27 (0.7)	37 (0.9)
Decrease in Hb ≥ 2 g/dL	28 (0.7)	42 (1.0)
Transfusion of ≥2 units of whole blood or packed red blood cells	18 (0.4)	25 (0.6)
Clinically relevant non-major bleeding	357 (8.6)	357 (8.7)
Any bleeding	1169 (28.3)	1153 (28.0)

* Bleeding event occurred after randomization and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule in EINSTEIN DVT and EINSTEIN PE studies: XARELTO 15 mg twice daily for 3 weeks followed by 20 mg once daily; enoxaparin/VKA [enoxaparin: 1 mg/kg twice daily, VKA: individually titrated doses to achieve a target INR of 2.5 (range: 2.0-3.0)]

‡ Treatment-emergent major bleeding events with at least >2 subjects in any pooled treatment group

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥2 units of whole blood or packed red blood cells

Reduction in the Risk of Recurrence of DVT and/or PE: EINSTEIN CHOICE Study: In the EINSTEIN CHOICE clinical study, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 1% for XARELTO 10 mg, 2% for XARELTO 20 mg, and 1% for acetylsalicylic acid (aspirin) 100 mg. The mean duration of treatment was 293 days for XARELTO 10 mg-treated patients and 286 days for aspirin 100 mg-treated patients.

Table 3 shows the number of patients experiencing bleeding events in the EINSTEIN CHOICE study.

Table 3: Bleeding Events* in EINSTEIN CHOICE

Parameter	XARELTO† 10 mg N=1127 n (%)	Acetylsalicylic Acid (aspirin)† 100 mg N=1131 n (%)
Major bleeding event	5 (0.4)	3 (0.3)
Fatal bleeding	0	1 (<0.1)
Non-fatal critical organ bleeding	2 (0.2)	1 (<0.1)
Non-fatal non-critical organ bleeding§	3 (0.3)	1 (<0.1)
Clinically relevant non-major (CRNM) bleeding¶	22 (2.0)	20 (1.8)
Any bleeding	151 (13.4)	138 (12.2)

* Bleeding event occurred after the first dose and up to 2 days after the last dose of study drug. Although a patient may have had 2 or more events, the patient is counted only once in a category.

† Treatment schedule: XARELTO 10 mg once daily or aspirin 100 mg once daily.

§ Major bleeding which is not fatal or in a critical organ, but resulting in a decrease in Hb ≥ 2 g/dL and/or transfusion of ≥ 2 units of whole blood or packed red blood cells.

¶ Bleeding which was clinically overt, did not meet the criteria for major bleeding, but was associated with medical intervention, unscheduled contact with a physician, temporary cessation of treatment, discomfort for the patient, or impairment of activities of daily life.

In the EINSTEIN CHOICE study, there was an increased incidence of bleeding, including major and CRNM bleeding in the XARELTO 20 mg group compared to the XARELTO 10 mg or aspirin 100 mg groups.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 4.

Table 4: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N=4487 n (%)**	**N=4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N=3281 n (%)**	**N=3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N=1206 n (%)**	**N=1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.

† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions: Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in the EINSTEIN DVT and EINSTEIN PE studies are shown in Table 5.

Table 5: Other Adverse Reactions* Reported by ≥1% of XARELTO-Treated Patients in EINSTEIN DVT and EINSTEIN PE Studies

Body System Adverse Reaction		
EINSTEIN DVT Study	**XARELTO 20 mg N=1718 n (%)**	**Enoxaparin/VKA N=1711 n (%)**
Gastrointestinal disorders		
Abdominal pain	46 (2.7)	25 (1.5)
General disorders and administration site conditions		
Fatigue	24 (1.4)	15 (0.9)
Musculoskeletal and connective tissue disorders		
Back pain	50 (2.9)	31 (1.8)
Muscle spasm	23 (1.3)	13 (0.8)
Nervous system disorders		
Dizziness	38 (2.2)	22 (1.3)
Psychiatric disorders		
Anxiety	24 (1.4)	11 (0.6)
Depression	20 (1.2)	10 (0.6)
Insomnia	28 (1.6)	18 (1.1)
EINSTEIN PE Study	**XARELTO 20 mg N=2412 n (%)**	**Enoxaparin/VKA N=2405 n (%)**
Skin and subcutaneous tissue disorders		
Pruritus	53 (2.2)	27 (1.1)

* Adverse reaction with Relative Risk >1.5 for XARELTO versus comparator

Non-hemorrhagic adverse reactions reported in ≥1% of XARELTO-treated patients in RECORD 1-3 studies are shown in Table 6.

XARELTO® (rivaroxaban) tablets

Table 6: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

Body System Adverse Reaction	XARELTO 10 mg N=4487 n (%)	Enoxaparin† N=4524 n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* Adverse reaction occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication

† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of XARELTO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis, thrombocytopenia

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, hepatitis (including hepatocellular injury)

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

DRUG INTERACTIONS

General Inhibition and Induction Properties: Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Combined P-gp and strong CYP3A4 inhibitors increase exposure to rivaroxaban and may increase the risk of bleeding. Combined P-gp and strong CYP3A4 inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events.

Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Interaction with Combined P-gp and Strong CYP3A4 Inhibitors: Avoid concomitant administration of XARELTO with known combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole and ritonavir) *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with XARELTO as the change in exposure is unlikely to affect the bleeding risk *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Interaction with Combined P-gp and Moderate CYP3A4 Inhibitors in Patients with Renal Impairment: XARELTO should not be used in patients with CrCl 15 to <80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A4 inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems: Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and NSAIDs/Aspirin: Coadministration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid concurrent use of XARELTO with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: The limited available data on XARELTO in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Consider the benefits and risks of XARELTO for the mother and possible risks to the fetus when prescribing XARELTO to a pregnant woman *[see Warnings and Precautions]*.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations: *Disease-Associated Maternal and/or Embryo/Fetal Risk:* Pregnancy is a risk factor for venous thromboembolism and that risk is increased in women with inherited or acquired thrombophilias. Pregnant women with thromboembolic disease have an increased risk of maternal complications including pre-eclampsia. Maternal thromboembolic disease increases the risk for intrauterine growth restriction, placental abruption and early and late pregnancy loss.

Fetal/Neonatal Adverse Reactions: Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.

Labor or Delivery: All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery *[see Warnings and Precautions]*. The risk of bleeding should be balanced with the risk of thrombotic events when considering the use of XARELTO in this setting.

Data: *Human Data:* There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Post-marketing experience is currently insufficient to determine a rivaroxaban-associated risk for major birth defects or miscarriage. In an *in vitro* placenta perfusion model, unbound rivaroxaban was rapidly transferred across the human placenta.

XARELTO® (rivaroxaban) tablets

Animal Data: Rivaroxaban crosses the placenta in animals. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg during the period of organogenesis. This dose corresponds to about 14 times the human exposure of unbound drug. In rats, peripartal maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

Lactation: Risk Summary: Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. Rivaroxaban and/or its metabolites were present in the milk of rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XARELTO and any potential adverse effects on the breastfed infant from XARELTO or from the underlying maternal condition *(see Data)*.

Data: *Animal data:* Following a single oral administration of 3 mg/kg of radioactive [^{14}C]-rivaroxaban to lactating rats between Day 8 to 10 postpartum, the concentration of total radioactivity was determined in milk samples collected up to 32 hours post-dose. The estimated amount of radioactivity excreted with milk within 32 hours after administration was 2.1% of the maternal dose.

Females and Males of Reproductive Potential: Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In EINSTEIN CHOICE, approximately 39% were 65 years and over and about 12% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14) in full Prescribing Information]*.

Renal Impairment: In pharmacokinetic studies, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Nonvalvular Atrial Fibrillation: In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Patients with End-Stage Renal Disease on Dialysis: Clinical efficacy and safety studies with XARELTO did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of XARELTO 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamic activity similar to those observed in the ROCKET AF study *[see Clinical Pharmacology (12.2, 12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.

Treatment of DVT and/or PE and Reduction in the Risk of Recurrence of DVT and/or PE : In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Prophylaxis of DVT Following Hip or Knee Replacement Surgery: The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with CrCl 30 to 50 mL/min and reported a possible increase in total venous thromboemboli in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Avoid the use of XARELTO in patients with CrCl <30 mL/min.

Hepatic Impairment: In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of XARELTO in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable *[see Warnings and Precautions and Clinical Pharmacology (12.3) in full Prescribing Information]*. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778
or
Bayer AG
51368 Leverkusen, Germany

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

 cp-49791

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New, More Potent Formulation of HyperRAB

by **MICHELE KAUFMAN, PHARMD, BCGP**

HyperRAB® 300 IU/mL is a higher-potency formulation of a previously Food and Drug Administration–approved rabies immune globulin (RIG; human), HyperRAB S/D, also available as 1,500 IU/10 mL.[1] The original HyperRAB S/D is available as 300 IU/2 mL and 1,500 IU/10 mL.

Administration and Dosing

RIG is administered as postexposure prophylaxis along with the rabies vaccine in people with suspected rabies exposure.[2] RIG provides passive immunity until active immunity with the rabies vaccine is recognized. RIG should not be given to anyone who has been previously immunized with rabies vaccine and has a confirmed adequate rabies antibody titer.

For unvaccinated people, the combination of rabies vaccine and RIG is recommended for bite and non-bite exposures, regardless of the time between exposure and postexposure prophylaxis initiation. Do not give RIG beyond day 7 after receiving the rabies vaccine because an antibody response to the vaccine is presumed to have already occurred.

RIG is administered locally via wound infiltration as a single dose of 20 IU/kg. If feasible, the entire dose should be infiltrated around and into the wound(s). Any remaining RIG volume should be administered intramuscularly at a site distant from the vaccine administration site. Infants, children, and adolescents should all be dosed with 20 IU/kg. This new formulation provides a greater concentration per volume of anti-rabies virus antibodies to go into delicate wounds such as those of the face, with the potential for fewer injections, making it less uncomfortable for younger patients.

ILLUSTRATION: CHRIS WHISSEN & SHUTTERSTOCK.COM

Adverse Reactions and Precautions

Adverse reactions include injection site pain and headache. Hemolysis can occur in patients with non-O blood groups and underlying inflammatory conditions. Anaphylaxis/hypersensitivity reactions can also occur. Use cautiously in patients at an increased risk for thrombosis or with a history of bleeding disorders and/or patients on anticoagulant therapy.

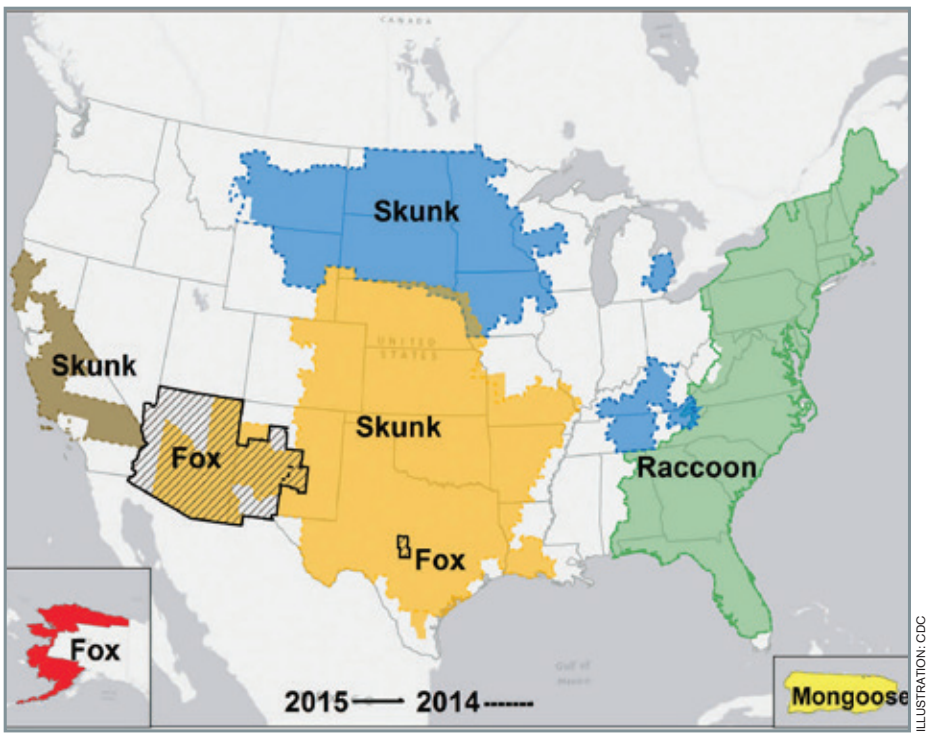

ILLUSTRATION: CDC

Figure 1: Distribution of major rabies virus variants among mesocarnivores in the United States and Puerto Rico, 2008–2015.

Product Safety

Because HyperRAB is made from human plasma, it may contain infectious agents and, theoretically, the variant Creutzfeldt-Jakob disease agent. Other unknown infectious agents may be present in RIG. Administer cautiously to patients with a prior history of systemic allergic reactions following human immunoglobulins.

Other Rabies Immune Globulin Products2

- Imogam Rabies-HT injection 300 IU/2 mL and 1,500 IU/10 mL
- Kedrab injection 300 IU/2 mL and 1,500 IU/10 mL (latex- and pyrogen-free)

Price2

- HyperRAB 300 IU/mL (1 mL) and HyperRAB S/D 300 IU/2 mL: $852.14
- HyperRAB 1,500 IU/5 mL (5 mL) and HyperRAB S/D 300 IU/2 mL: $3,889.42
- Imogam Rabies-HT 300 IU/2 mL: $867.05
- Imogam Rabies-HT 1,500 IU/10 mL: $3,977.23
- Kedrab injection: cost not known

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CLINICAL PERSPECTIVE

"A Bat Flew Into My Head"

New rabies postexposure prophylaxis options

by DAVID A. TALAN, MD, FACEP, FIDSA

An emergency physician friend texted me about whether I thought he should get rabies postexposure prophylaxis (RPEP). He said that while he was out for an evening stroll, a bat flew into him, hitting him in the forehead not just once but twice. Although he could not find evidence of a bite or wound, he wondered what he should do.

Emergency physicians are presented with these types of patient questions frequently, usually related to dog bites but from other types of exposures, too, with various degrees of circumstantial bite evidence. The calculous around the decision to give RPEP is portentous. Rabies, with extremely rare exceptions, is an untreatable fatal disease, but if the exposure is identified and prophylaxed, it's also 100 percent preventable.

In some cases, the animal can be captured and observed or killed and tested immediately, and a new polymerase chain reaction test is likely to be available soon to facilitate rapid animal testing. However, when the animal is unavailable, the decision for RPEP is made in the emergency department. Over time, the RPEP regimen has gotten easier, four instead of five vaccinations, but no less expensive. The cost of the rabies immune globulin (RIG) and vaccine regimen is in the neighborhood of $4,000 to $5,000 total based on Red Book pricing, although charges have been noted to vary greatly on hospital bills.[1] There's also a new RIG formulation called HyperRAB, which has some advantages. Before we get back to the answer to my friend's question, let's review the latest RPEP recommendations and options.[2]

Treatment

Initially, it's most important to thoroughly irrigate and clean the wound. Since incubation periods of more than one year have been reported in humans, when a likely exposure has occurred, RPEP should be given regardless of the length of the delay.

RIG, a pooled human donor product, should be given in the emergency department, infiltrating as much of the full 20 IU/kg

dose as possible into the subcutaneous tissue at the wound site and the remainder given intramuscularly, typically in the deltoid opposite the vaccine administration site. HyperRAB, approved in February 2018, is a more potent version of the previously licensed HyperRAB S/D (both Grifols Therapeutics, Inc.), Imogam Rabies-HT (Sanofi Pasteur SA), and Kedrab (Kedrion Biopharma and Kamada, Ltd). HyperRAB requires less volume to achieve the recommended 20 IU/kg dose, allowing more RIG to be delivered at the site of potential rabies virus inoculation.

For example, the concentration of older RIG formulations is 150 IU/mL. For a 75 kg person, 20 IU/kg requires 1,500 IU in 10 mL. Imagine trying to infiltrate a 10 mL syringe of RIG into the tip of a finger. Alternatively, the concentration of HyperRAB is 300 IU/mL, which in this example would equate to half of the previous amount, or 5 mL; it would still be difficult to get all of it in a finger wound, but twice as much could be injected. For my friend, this would represent the difference between having a small bump on his forehead or one that more resembles Pott's puffy tumor. According to Red Book prices, the new HyperRAB formulation costs the same as the older HyperRAB S/D and the other RIG products, about $3,200 for 1,500 IU.

If the price that hospitals and insurers negotiate is similar among formulations, pharmacies may decide to stock HyperRAB, both for its theoretical greater effectiveness by allowing more immunoglobulin to be injected into the wound and for the less pain associated with the remaining lower-volume intramuscular injection.

Rabies remains endemic in raccoons, foxes, and skunks regionally in the United States (see Figure 1) and bats everywhere, and each year between 60 and 70 dogs and more than 250 cats are found rabid. However, only 23 cases of human rabies have been reported in the past decade compared to 60,000 cases annually worldwide, and none were due to RPEP failure. So it does not appear that our previously available RIG preparations have been ineffective. RPEP failures have rarely occurred due to RIG injected only intramuscularly and not into all the wounds.

There are potential drawbacks with higher-concentrated RIG. For example, for extensive wounds, the Advisory Committee on Immunization Practices recommends diluting RIG to ensure sufficient volume to infiltrate all of the wounds. In this scenario, the doubly concentrated formulation might require additional dilution, which must be done with 5 percent dextrose in water rather than normal saline. Thus, the standard concentration might be preferred in this situation. Also, the change in concentration may increase the risk of miscalculating the dosage if clinicians mistakenly use the previous standard concentration.

In addition to RIG, rabies vaccine should be administered intramuscularly in the deltoid area, 1 mL initially (day 0) and then again on days 3, 7, and 14 (also day 28 if the patient is immunocompromised). Two licensed vaccines are currently available in the United States: human diploid cell vaccine (Imovax Rabies, Sanofi Pasteur) and purified chick embryo cell vaccine (RabAvert, Novartis Vaccine and Diagnostics).

Vaccine should not be administered in the gluteal area because this may result in lower antibody titers. The deltoid is the only acceptable intramuscular site of vaccine administration in adults and older children; the outer thigh can be used in young children. Vaccines cost about $300 per dose. Vaccine shortages have occurred, and the Centers for Disease Control and Prevention (CDC) maintains a website for rabies vaccine availability, www.cdc.gov/rabies/resources/availability.html.

Because of the cost, some public health experts have been concerned about ED overprescription. However, when we studied RPEP from more than 2,000 animal exposures presenting to our CDC EMERGEncy ID NET sites, we found that emergency physicians were in fact conservative in their use based on local guidelines.[3]

Back to our friend, the emergency physician "batted" in the head. Human rabies epidemiology in the United States helps provide the answer.

According to the CDC, the most common rabies virus variants responsible for human rabies in the United States are bat-related.[2] During 1990–2007, 34 bat-associated human cases of rabies were reported in the United States. In six cases, a bite was reported; in two cases, contact with a bat and a probable bite were reported; in 15 cases, physical contact was reported (eg, the removal of a bat from the home or workplace or the presence of a bat in the room where the person had been sleeping), but no bite was documented; and in 11 cases, no bat encounter was reported. In these cases, an unreported or undetected bat bite remains the most plausible hypothesis because the genetic sequences of the rabies virus closely matched those of specific species of bats.

Rabid bats are more aggressive and have difficulty flying. The little sono-geeks do not normally fly flat into the foreheads of people, not once and especially not twice. So the bat in question was very likely rabid. And since bat bites can be imperceptible, this type of exposure requires RPEP. When in doubt, call the local health department, which is available 24-7 for these sometimes difficult and expensive ED decisions. My friend's hospital bill was $16,240.

Acknowledgment: I *would like to thank Dr. Brett Petersen and Dr. Andrea McCollum at the CDC for their review and suggestions.*

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SKEPTICS' GUIDE

CONTINUED FROM PAGE 30

Certainty in the Evidence

OUTCOME	NUMBER OF STUDIES	CERTAINTY
Reduction in pain scores	6 RCT and 2 observational	Very low
Need for rescue analgesia	5 RCT and 2 observational	Very low
Incidence of adverse events	4 RCT and 2 observational	Very low

Evidence-Based Medicine Commentary

1. **Search Strategy:** This was an excellent example of how to do a good search.
2. **Quality of Evidence:** The quality of evidence was low due to methodological problems, risk of bias, inconsistency, small studies, and imprecision. There was so much heterogeneity that they correctly did not perform a meta-analysis.
3. **Hierarchy of Evidence:** There is a pyramid of evidence for evidence-based medicine (see Figure 1). On the bottom is background information and expert opinion and at the top is the systematic review. However, in this case, when the quality of evidence is so poor, I would suggest a well-done RCT gets us closer to the truth than a number of low-quality RCTs and observational studies.

Bottom Line

The routine use of IV lidocaine for analgesia in the emergency department cannot be supported based on the current strength of available evidence.

There is limited current evidence to define the role of intravenous lidocaine as an analgesic for patients with acute renal colic and critical limb ischemia pain in the ED.

Case Resolution

The patient is advised that physicians have tried lidocaine as a non-opioid analgesic, but that the research really does not support its effectiveness or safety at this time. The physician recommends IV morphine again, and the patient arranges another way home.

Thank you to Dr. Sergey Motov, an emergency physician in the department of emergency medicine at Maimonides Medical Center in New York City.

Remember to be skeptical of anything you learn, even if you heard it on the Skeptics' Guide to Emergency Medicine.

MYTHS IN EMERGENCY MEDICINE

Rooted in culture, based on tradition

by KEVIN M. KLAUER, DO, EJD, FACEP

New Data Haven't Changed Ophthalmology's Myopic View of Topical Anesthetics for Corneal Abrasions

For decades, emergency physicians have challenged the premise that topical anesthetics used for a short duration of time (eg, hours to days) couldn't possibly harm patients. This seems like a reasonable, common-sense argument, which should prompt widespread adoption. However, emergency physicians who were bold enough to go rogue on this topic were met with great resistance. Apparently, commonsense is no match for the myopic dogma about this topic in the ophthalmological community.

Perhaps, randomized controlled trials would be necessary to unequivocally demonstrate that the safety of the short-term use of topical anesthetics (eg, tetracaine) for corneal abrasions.

The Data

The roots of dogmatism and myth propagation run deep—in this case, very deep. Three credible studies, which were published in 2014, more than adequately reflect the safety of the short-term use of tetracaine for corneal abrasions. The first, was published by Waldman et al in 2014.[1] This prospective, randomized, double-blind study of 116 patients compared undiluted tetracaine (1%) to saline in patients presenting with uncomplicated corneal abrasions during a 12-month period. The drops could be applied every 30 minutes while the patient was awake for a maximum of 24 hours. No tetracaine-attributable complications were noted in the treatment group, and there was no statistically significant difference in delayed corneal healing (defined as fluorescein update at 48 hours) between the two groups (23.9 percent for tetracaine versus 21.3 percent for saline).

In 2015, Puls et al performed a systemic review and meta-analysis that included two randomized trials.[2] They reported no significant differences in pain, persistent symptoms, or corneal healing. Although their data reflected an odds ratio for delayed healing of 1.31 for those receiving topical anesthetics for 72 hours or less, suggesting 31 percent greater odds for delayed healing with topical anesthetics, the bottom line is that no complications from treatment were noted. Also published in 2015 was a systematic review that included the two randomized trials Puls identified, as well as four additional studies evaluating topical anesthetic use in patients following photorefractive keratectomy.[3] They reached similar conclusions: "Our literature search produced two emergency department-based, randomized, double-blind, placebo-controlled studies on human patients with corneal abrasions. Additionally, we found four studies that investigated the application of topical anesthetics in patients who underwent photorefractive keratectomy. All six studies demonstrated that a short course of dilute topical anesthetic provided efficacious analgesia without adverse effects or delayed epithelial healing."

Finally, this year Waldman published a study larger than the prior work in 2014.[4] This was a well-done study of 1,576 patients with corneal abrasions, of which 532 were determined to be "simple" as opposed to "complicated." The relative risks for ED return visit and fluorescein staining (both indications of persistent symptoms) were 1.67 and 2.53, respectively. However, when considering only simple corneal abrasions, the numbers neutralized to 1.16 and 0.77. Most important, the complications were too rare to model, and thus there was no evidence that the short-term use (24 hours) of non-dilute tetracaine was unsafe. Will our ophthalmology colleagues be satisfied? Past experience predicts future expectations.

A Change in Practice?

These data should suffice to put this question to rest. Unfortunately, dogma may create an irrational conviction to unfounded "facts." For example, three ophthalmologists wrote a very critical rebuttal to Waldman's 2014 study.[5] "While tetracaine temporarily anesthetizes pain, its routine usage to treat traumatic corneal abrasions in an emergency department is dangerous and can lead to blinding ocular complications."

What evidence did they offer to support this hysteria? None, except for one study about chloramphenicol ointment, which was used to establish a low rate of corneal ulcer (0.26 percent) from corneal abrasions in Nepal, reporting more complications in Waldman's tetracaine group.[6] However, none of Waldman's patients ever developed corneal ulcers. The ophthalmologists also cited a case report of eight patients who developed corneal defects, stromal opacity, or ring-shaped infiltrates. However, only one patient was treated for a corneal abrasion while the others had more severe pathology and the mean duration of topical anesthetic use was 14.8 days ± 7.78 days.[7]

Their final evidence was from a 1990 article titled, "Topical Anesthetic Abuse." Really? Is tetracaine a drug of abuse? This was a case report of six patients with complications, reportedly secondary to prolonged anesthetic use.[8] Finally, perhaps their greatest criticism reflects a negative bias about emergency physicians. "The methodology used to diagnose corneal abrasions is ambiguous. None of the corneal evaluations were performed by an ophthalmologist, and some of the evaluations were not even done by a physician."[5] It is maddening to consider that in 2014, some ophthalmologists didn't feel emergency physicians were qualified to diagnose corneal abrasions. Clearly, the evidence they were challenging was far superior to anything they presented. With dogma as thick as fog, the only answer must be that the duration and volume of "evidence" must have shaped generations of ophthalmologists, resulting in the indiscriminate and irrational challenge of alternative perspectives, despite evidence supporting new thinking.

Anesthetic keratopathy from prolonged and uncontrolled use has been reported as far back as 1956.[9,10] Since that time, many articles have been published but were editorials based on historical opinion as opposed to evidence, studies using mouse and rabbit corneas, and an impressively long list of case reports. The volume is nearly as impressive as the 60-plus years of poor-quality or nonexistent evidence used to perpetuate this myth.

Emergency physicians are efficient in our work and our thinking. Four years and a small number of good-quality studies, and we have our answer. Short-term topical anesthetics have never been proven to cause injury or delay healing, and 24-hour use in simple corneal abrasions is certainly safe, particularly with dilution.[3] It's time to open the eyes of some ophthalmologists who believe that years of dogma and reams of poor evidence is a substitute for common sense and a small number of good-quality studies.

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OPIOIDS | CONTINUED FROM PAGE 28

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SEND US YOUR QUESTIONS!

In future articles in this series, we will delineate the best practices for treatment and approach in the emergency department. If you have questions or ideas, feel free to send them our way at schwarze@wustl.edu. Until then, let data, science, and math rule the day!

SERVING UP THE BEST EM TWEETS

THE FEED

DR. FAUST is an instructor at Harvard Medical School and an attending physician in the department of emergency medicine at Brigham & Women's Hospital, Boston. Follow him on Twitter @jeremyfaust.

EM Doc Hold'em

Emergency physician Dr. Joseph Young is a World Series of Poker phenom

by JEREMY SAMUEL FAUST, MD, MS

Joseph Young, DO, is the medical director for the emergency department at Baylor University Medical Center in Dallas. In July 2018, he placed 343 out of 7,784 entrants in the World Series of Poker's prestigious Texas Hold 'em Main Event, held in Las Vegas, taking home $37,705 in cash. The tournament entry fee was a staggering $10,000, but the winning player earned over $9 million. We recently spoke about poker, emergency medicine, and wellness.

PHOTO: JOSEPH YOUNG

Dr. Joseph Young with his winnings from the World Series of Poker's Texas Hold 'Em Main Event.

JF: How often do you play and when did you start playing seriously?

JY: I started in high school. As an undergraduate in Tampa, there was a casino nearby. They only had limit games. I would go and read books and play. During residency [at the University of Texas Southwestern Medical School in in Dallas] I started playing some cash games and small tournaments. When I finished residency, I found a bunch of hospital colleagues at work who liked to play, and we formed a home poker league. In fact, our sixth season is starting this Sunday. We had 10 players, and we played over 10 months for $100 per month. The winner of the league takes the entire $10,000 pot and uses it for the World Series of Poker entry fee. This year, we are up to 24 players, so we can send two players to the Main Event. Seventy percent of any winnings goes to the winning player and the remaining 30 percent is split among the other players in the league.

JF: How many times have you seen the film "Rounders"?

JY: Once!

JF: And "Molly's Game"?

JY: That's a great film.

JF: Was this summer your first time playing in a professional poker tournament?

JY: This was actually my second time in the World Series of Poker Main Event. I won the league last year, so I got the entry fee. This year, I paid my own way.

JF: How did last year go?

JY: Last year I did terribly; I busted on the first day. I lost three sets over sets to the same guy. Terrible. [Note: This means he had three of a kind, but that the other player had a higher three of kind. Having it happen three times to the same player is extremely bad luck.]

JF: You weren't left with a bad taste?

JY: The tournament structure is the best in the world. You start with 50,000 chips versus 10,000 to 20,000 in most professional tournaments, and the blind levels are two hours long. [Note: This means that the required rotating antes are low with respect to the size of the players' initial chip counts and they do not increase that frequently. This makes the game less prone to luck.] It takes patience and time. It takes mental strength and focus.

JF: Did you do anything special to prepare for the World Series?

JY: My close buddies and I bought a subscription to a website to review strategies, how to play certain positions and how to extract the most from other players. I also watched Daniel Negreanu's Masterclass online. Chris Moorman's *Book of Poker* was also helpful. These resources really help with game theory for optimal strategies.

JF: How long did you have to be in Las Vegas for the tournament?

JY: Seven days, but I blocked off two weeks just in case; that's how long you need to be available.

JF: I like the confidence!

JY: Yeah, but I only booked the hotel for the first three days. Once I survived day one, I had to book another hotel night. Vegas was packed because there was an Ultimate Fighting Championship event happening too. So, I had to switch hotels which was a little stressful.

JF: Walk us through a day at the World Series of Poker.

JY: I try to be as healthy as possible: Get a minimum of eight hours of sleep, don't set an alarm other than an hour before the tournament starts, just to be safe, eat breakfast (I eat a healthy egg white omelet), drink some coffee to stimulate my mind.

JF: How do you even register?

JY: You can actually carry $10,000 in cash and just register the day of. Or you can sign up a well in advance. I did it ahead of time, because I didn't want to get robbed while having 10 grand on me. If you'd paid ahead of time, you get your seat assignment pretty quickly.

JF: How long are you playing at a time?

JY: Two hours of play, followed by a 30-minute break. Then, there's one main dinner break. Depending on the day and the ESPN coverage, you don't always know when you'll get a dinner break. Each day is 12.5 hours.

JF: So you survived day one. The number of players remaining gets smaller. Did they make you switch tables?

JY: On day two, I was switched three times.

JF: Can you feel the difference between playing against a professional versus an amateur?

JY: Yes, without a doubt. You fish out info from people over time. For example, the guy next to me on day one had an interesting story. His buddy had died, and he was only was there because his friend had wanted his friends to the play the Main Event. It was in his will. So, he was very nice, but he didn't really know what he was doing. In general, pros and amateurs play very differently. Pros often make smaller pre-flop bets [Note: bets before any community cards are placed on the table]. Even most amateurs know which cards are good starting hands, but it gets trickier after the flop. When pros know you are an amateur, they are more likely to come after you and put you in difficult spots.

JF: Did any skills you have from being an emergency physician help you at the World Series of Poker?

JY: We work in such a high stress environment and this is just a game, so you can be relaxed. Also, we see a lot of BS. People manipulating us for drugs, not telling us the full story, etc. You learn to observe behavior which you can apply to poker. You can figure out a lot about someone by how they sit or by interpreting their body language. If, all of a sudden, a player is breathing fast or if you can see their carotids or radial pulse just going like crazy ...

JF: They are nervous, but is it because they are bluffing or because they have a huge hand?

JY: You have to put that information in the context of their other behavior and actions.

JF: Are you a math-based player or a gut-based "gestalt" player?

JY: Definitely more math, positional. [Note: Positional refers to changing your style of play depending on where you are sitting with respect to the players who have been forced to ante up in a particular hand.]

JF: What's the highest hand you had in terms of value?

JY: Four of a kind was by far my best hand.

JF: What's the worst mistake you made?

JY: I truly didn't feel like I ever made a very bad decision. Overall, I just got whittled down at the end. There's one hand I did not play that I regretted.

JF: Once you were officially guaranteed to be "in the money," was your goal to reach a certain amount or to last as long as possible?

JY: The goal is to win it, for sure. We are blessed to have the careers we do. Winning $20,000 won't change our lives. The goal is to make the final table [Note: The final table of nine players are guaranteed $1 million in prize money each.]

JF: Once around 1,000 players were left, the emergency medicine community started to notice your run. I started checking in on your progress online, as did many others, and we were rooting for you! What was it like feeling the love on Twitter and Facebook from the EM community?

JY: It was amazing. That EM Docs group on Facebook is legit. And the Twitter love was so great.

JF: Will you play in the World Series again?

JY: I'll definitely be back next year.

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A 4-Step Approach to Treating Alcohol Withdrawal

Don't miss this potentially fatal diagnosis

by **ANTON HELMAN, MD, CCFP(EM), FCFP**

Even though more than half a million patients are seen in U.S. emergency departments for alcohol withdrawal each year, this seemingly straightforward diagnosis is missed more often than we may believe.[1] Even when it is picked up, it is often mismanaged. Why?

We sometimes don't suspect it in the first place. For example, we may not think about alcohol withdrawal in the older patient who presents with delirium.[2] Second, the differential diagnosis is enormous, and the presentation overlaps with other common ED diagnoses such as sympathomimetic drug intoxication and sepsis. There is no lab test to rule in the diagnosis, and we sometimes get sidetracked by other concurrent medical, psychiatric, and traumatic issues.

Mismanagement of these patients may stem from a lack of ED training on this topic and be due to little standardization in management. There is, unfortunately, still a stigma associated with alcoholism, which may contribute to indifference to these patients by ED staff, and the medications used to treat alcohol withdrawal are often dosed incorrectly.[3] Mismanaged alcohol withdrawal can be fatal, and untreated severe withdrawal often ends up with your patient seizing and sometimes progressing to delirium tremens.[4]

Management of Alcohol Withdrawal Involves Four Steps

First, accurate diagnosis based on clinical features is paramount. Next, the use of a standardized, symptom-guided tool to assess symptom severity and guide treatment is important. Third, ensure that patients are fully treated prior to ED discharge, and fourth, provide a pathway to support for patients who are trying to quit.

1. Tremor is central to the diagnosis of alcohol withdrawal.

The diagnosis of alcohol withdrawal should be thought of as a clinical diagnosis of exclusion after infection, other toxidromes (ie, sympathomimetics, anticholinergics, toxic alcohols), serotonin syndrome, neuroleptic malignant syndrome, hypertensive crisis, acute pain, and thyrotoxicosis have been considered. There must be clear evidence of recent cessation or reduction of alcohol after high-dose regular use. Symptoms from alcohol withdrawal usually start within six to eight hours after the blood alcohol level decreases, peak at 72 hours, and diminish by days five to seven of abstinence. Delirium tremens can occur anytime from three to 12 days after abstinence.

The tremor of alcohol withdrawal is central to the diagnosis. It is important to understand the three key features of alcohol withdrawal tremor. It is an *intention* tremor (there is no tremor at rest, but when you ask the patient to extend their hands or arms, you will see a fine motor tremor) that is *constant* and *does not fatigue* with time. Other symptoms associated with alcohol withdrawal include gastrointestinal upset, anxiety, nausea/vomiting, diaphoresis, tachycardia, hypertension, and headache. If malingering is suspected, ask the patient to protrude their tongue. A tongue tremor is impossible to feign and is thought to be a more sensitive sign of alcohol withdrawal than hand tremor.

There are no lab tests that are diagnostic for alcohol withdrawal. A serum ethanol level should be considered only if you are unsure of the diagnosis. Even then, there is no single ethanol level at which withdrawal is impossible. Chronic alcohol users may experience alcohol withdrawal at serum ethanol levels that are intoxicating to the naive drinker. In mild cases of withdrawal, blood work is rarely helpful and is unlikely to change management. However, in patients with severe alcohol withdrawal, especially patients with delirium tremens, blood work can help rule out other causes of delirium.

There are no lab tests that are diagnostic for alcohol withdrawal. A serum ethanol level should be considered only if you are unsure of the diagnosis. Even then, there is no single ethanol level at which withdrawal is impossible.

2. Use a standardized, clinically guided approach to assess severity and guide treatment.

The Clinical Institute Withdrawal Assessment Scale for Alcohol (CIWA-Ar) protocol is a 10-item scale. It has been well validated in patients with alcohol withdrawal, improving the quality and consistency of care, but should not be used for patients with delirium tremens or as a diagnostic tool.[5]

The CIWA-Ar calls for patients to be assessed hourly and treated if the total score is 10 or greater. When two sequential scores are less than 10, discharge may be considered. Protocols using the CIWA-Ar help to standardize care, ensure clinicians identify the appropriate clinical features, and monitor treatment response. CIWA-Ar assesses 10 clinical features: nausea and vomiting, paroxysmal sweats, agitation, anxiety, visual disturbances, tremor, tactile disturbance, headache, auditory disturbances, and orientation and clouding of the sensorium.

Some clinicians find the CIWA-Ar protocol too labor-intensive. The SHOT (**S**weating, **H**allucinations, **O**rientation, and **T**remor) protocol is a shorter one, which may be easier to implement in the emergency department. It is a four-item scale that correlates well with the CIWA-Ar score and takes about one minute to apply.[6]

3. Ensure that patients are fully treated prior to ED discharge.

If a patient has two sequential CIWA-Ar scores (two hours apart) less than 10 and there are no concerning risks for deterioration, consider discharging the patient from the emergency department. The patient's tremor should be minimal or resolved before discharge, regardless of the CIWA-Ar score, as those with significant tremor are at risk of complications of alcohol withdrawal if discharged from the emergency department.

Benzodiazepines are first-line medications for treating patients with alcohol withdrawal. A Cochrane meta-analysis found that benzodiazepines are at least as effective as alpha-blockers and carbamazepine at preventing seizures and delirium tremens.[7] The drug of choice is diazepam because it has a long half-life (100 hours) and carries a decreased risk of developing serious withdrawal symptoms once the patient is discharged. Diazepam also has a faster onset of action than lorazepam. Nonetheless, it is important to remember that diazepam should be avoided in patients with liver failure or a history of liver failure.

Use oral benzodiazepines in stable patients with mild withdrawal who are not vomiting (diazepam 5–10 mg by mouth for CIWA-Ar score 10–20). Use IV benzodiazepines allow-

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ing faster onset and easier titration in patients with severe withdrawal as these patients are at a higher risk of seizure (diazepam 10–20 mg IV for CIWA-Ar score greater than 20). Assess for response every five minutes in severe alcohol withdrawal, and repeat dosages as necessary. Some protocols suggest escalating dosages of diazepam by 10 mg every five minutes to a maximum of 40 mg per dose.[8]

There is no evidence that phenobarbital is superior to benzodiazepines for preventing complications of alcohol withdrawal.[9,10] While debate continues regarding the equivalency of phenobarbital and benzodiazepines, I do not recommend using phenobarbital alone for treatment of alcohol withdrawal, but consider its use as an adjunct with benzodiazepines after the patient has received the equivalent of 200 mg of diazepam and is still in severe withdrawal.

It is strongly discouraged that patients be provided a takeaway supply or prescription for benzodiazepines. The long half-life of diazepam will protect patients from developing serious symptoms of withdrawal, and if adequately treated in the emergency department, no additional medications will be required. Patients who are discharged from the emergency department with a prescription for benzodiazepines may be at increased risk for sedative overdose, drug-seeking behavior, and dependence.

4. Provide a pathway to support patients who are trying to quit.

Many patients in the emergency department with alcohol withdrawal are in a vulnerable state and may be ready to quit drinking. This is an opportune time for them to take the first steps on the pathway to recovery. I recommend counseling all ED patients whom you have treated for alcohol withdrawal by stating, "You need help for your serious alcohol problem. You can't do it on your own. There are effective treatments available to you. With treatment, the way you feel, your mood, social relationships, and work will be profoundly better."

Provide several options to patients and con-

sider starting patients who are interested in quitting on anti-craving medications such as naltrexone. Naltrexone blocks the release of endogenous endorphins, which are thought to be released during alcohol consumption, leading to positive reinforcement effects. Naltrexone, 50 mg by mouth once daily, has been shown to significantly reduce the rate of relapse as well as heavy drinking days.[11]

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HOW TO HANDLE ECG REIMBURSEMENT

by **DAVID FRIEDENSON, MD, FACEP**

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DR. FRIEDENSON is chair of ACEP's Coding and Nomenclature Committee and chief medical officer of Reventics in Denver.

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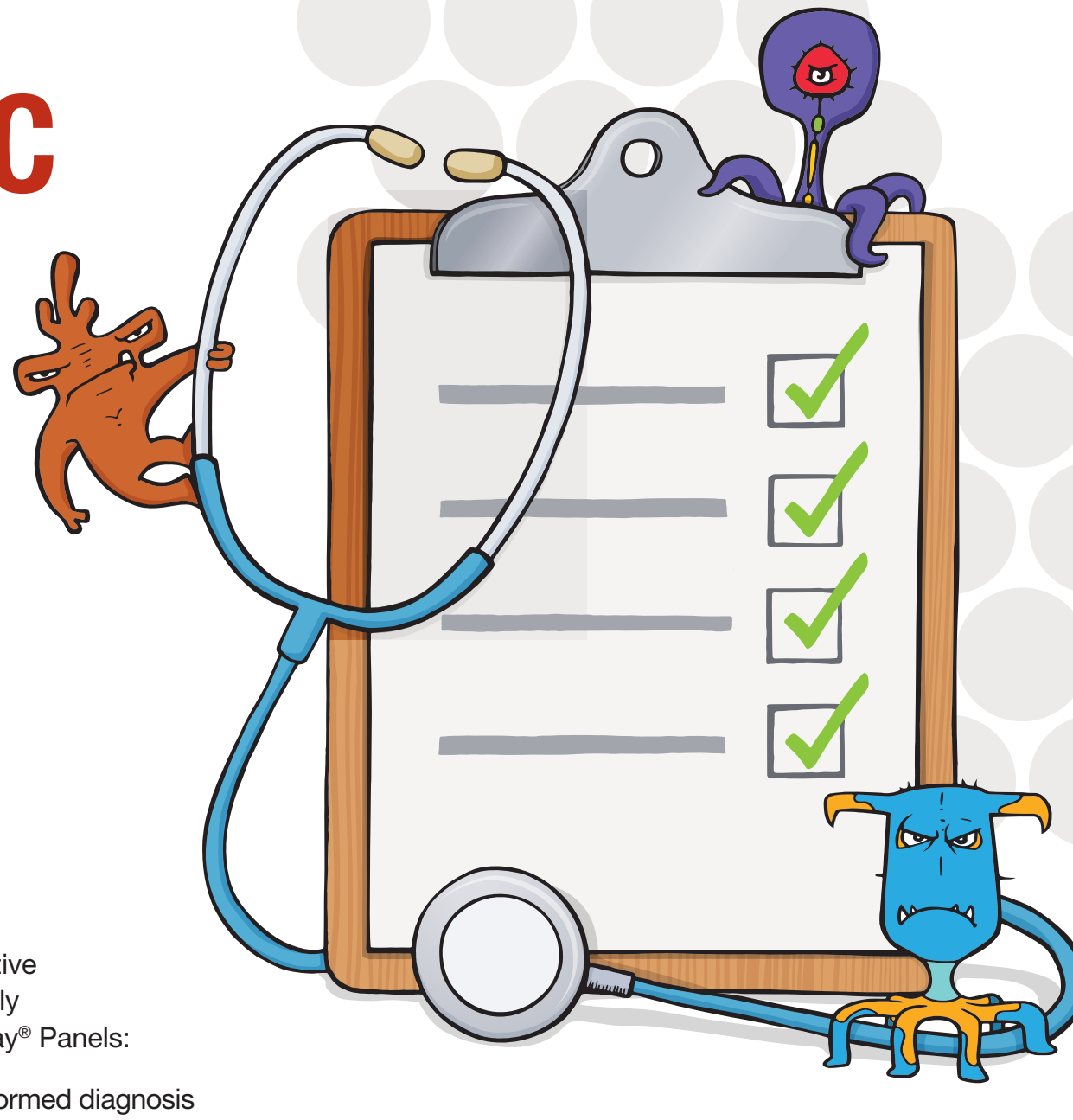

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