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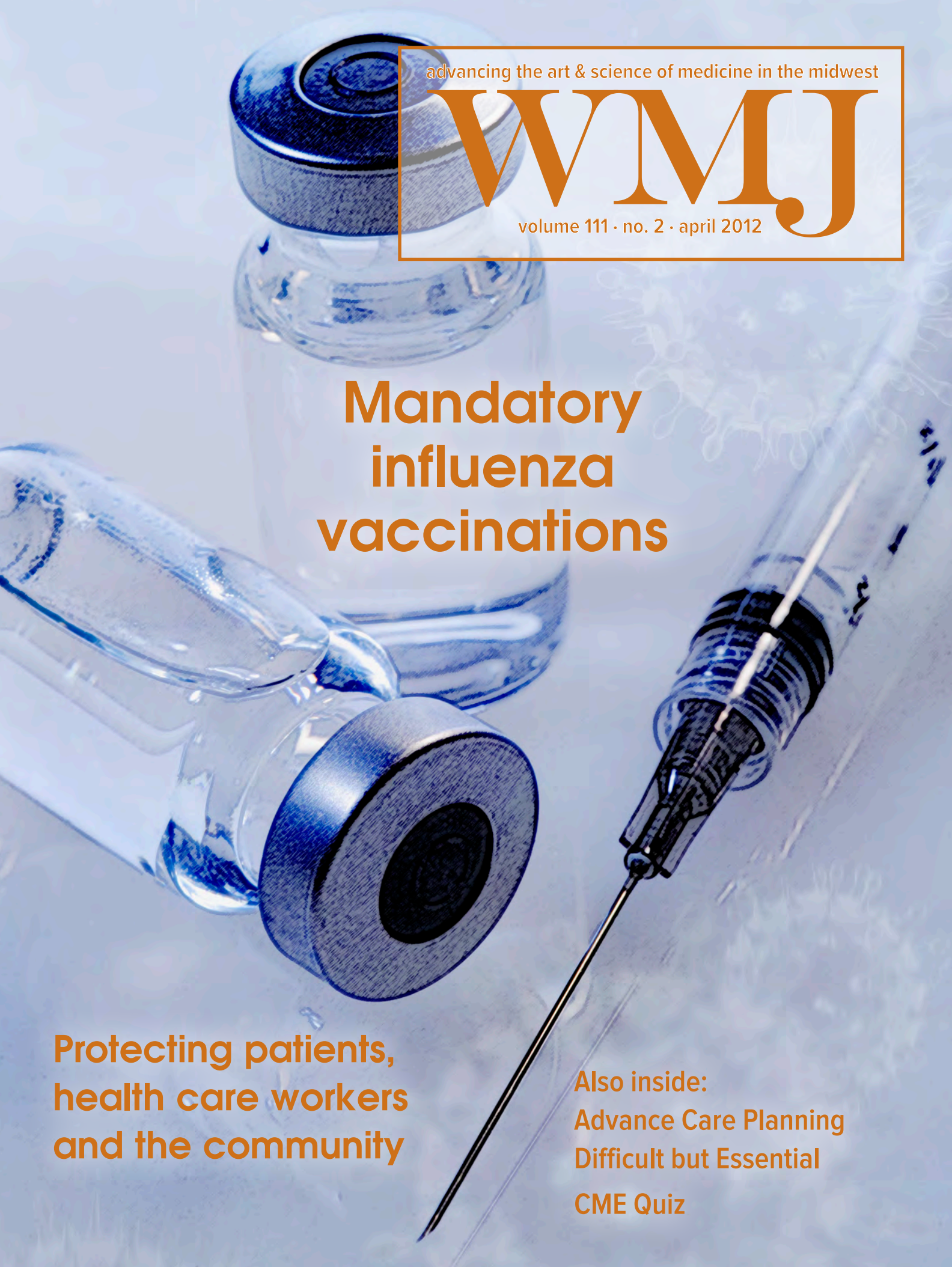

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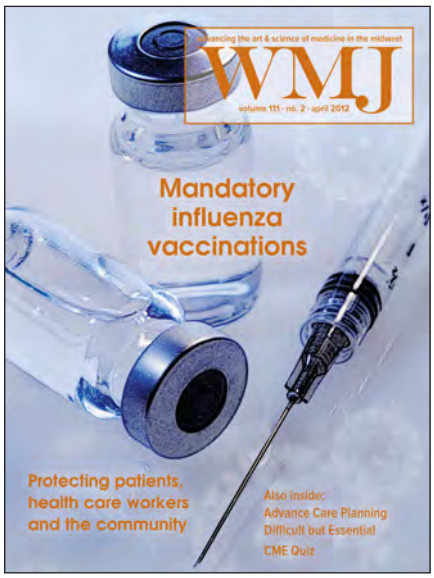

COVER THEME

Mandatory influenza vaccinations. Protecting patients, health care workers and the community

The interaction between required and voluntary when it comes to public health issues, such as mandatory vaccination, has been debated for decades. An article in this issue of *WMJ* shows how requiring influenza vaccines for health care workers at a large integrated health system has led to almost universal coverage, which is expected to decrease transmission in the workplace, illness in employees and lost work time.

Cover design by Mary Kay Adams-Edgette.

The mission of *WMJ* is to provide a vehicle for professional communication and continuing education for Midwest physicians and other health professionals. *WMJ* is published by the Wisconsin Medical Society.

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'Tis for Sore Feet

A.W. Myers, MD, Editor; J.P. McMahon, MD, Managing Editor

Editor's note: The following is from an editorial published in *WMJ*, Volume 10 (No. 8), January 1912, p. 467.

The time honored and more or less efficient remedies for "sore feet," alum and tannin are the essential constituents of a much advertised nostrum called "Tiz." This in brief, is the result of an analysis made in the chemical laboratory of the American Medical Association (J.A.M.A., Dec. 3, 1911, p. 1853). The laboratory's report contains the following amusing account of a testimonial for the nostrum:

"Of course, testimonials are used in true 'patent medicine' style. We learn, for instance, that Mrs. Crockett of Jeffersonville (state not mentioned), had been unable to walk downstairs for five years, 'except by stepping down on each step with one foot at a time'—the intimation being, apparently, that most people walk downstairs with both feet at a time. In any case, we learn that 'after the second treatment she walked downstairs one foot at a time.' The lady's husband, who sends in this testimonial, closes by saying: 'This is remarkable. Send five more boxes.' Doubtless by the time the fifth box is used Mrs. Crockett will be spry enough to slide down the bannisters."

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Effective Doctor-Patient Communication—A Hit or a Myth?

John R. Thurston, PhD

My credentials for writing this article and *The 20 Suggestions* referenced herein include many years as a patient, 29 years as a psychology professor, and over 30 years as a clinical psychologist working part-time within the medical establishment.

As a psychologist, I've long been interested in the basic communication skills of physicians. On a personal level, I've been very impressed by the ability of my many physicians to communicate their concerns and a great deal of complex information during the course of very brief consultations.

Is my positive view regarding the communicative capabilities of physicians shared by other patients? Hopefully, yes; but maybe not. It's possible that many patients have developed some unique and unrealistic notions regarding their illnesses and what to expect from their doctors. TV dramas, newspaper columns, advertisements, folklore, breaking news, and talks with other patients are among their influences. Patients may expect their physicians to be omniscient, omnipotent, compassion-compounded, and available 24/7. But in the real world of medicine, such persons are rare; and such unrealistic expectations could lead to routine disappointment for the patient and further complicate communication between the physician and patient.

Despite obstacles, most physicians probably believe they're good communicators. That might well be accurate, but there's always room for improvement. And a quest for such improvement can be an interesting and challenging project.

If a physician accepts this challenge, how should he or she go about it? A systematic inventory of one's communication skills is a good start. Amid their strengths, most physicians can find a few habits that could and should be modified or even eliminated. Perhaps a mere "tweaking" of one's communication skills is a responsible and reassuring first step.

Developed specially for physicians, *The 20 Suggestions* (available online at http://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/issues/wmj_v111n2/111no2_20questions.pdf) can serve as a helpful resource for such an undertaking. Each suggestion contains definitions, examples, and a format for change. Physicians seeking to improve their communication skills can first compare their behavior with those listed on this standard. Then, progressing in the spirit of the old song, they can "accentuate the positive" behaviors while "eliminating the negative" ones en route to personal and professional improvement. Such changes require both time and thought for their implementation.

Amid their strengths, most physicians can find a few habits that could and should be modified or even eliminated.

While physicians are the focus for these suggestions, with slight modifications this approach could be employed by other health care professionals as well.

Ultimately, the usefulness of *The 20 Suggestions* will be determined by the experience of physicians and other professionals who are willing to try them out.

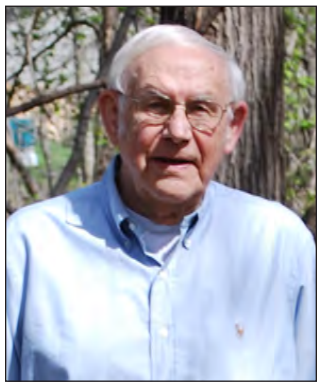
• • •

Dr Thurston is a clinical psychologist and professor emeritus of psychology at the University of Wisconsin-Eau Claire who resides in Eau Claire, Wis. He can be reached at thurstjr@charter.net.

Treffert's Work with 'Extraordinary People' Reaches Global Community

Kendi Parvin, *WMJ* Managing Editor

Curiosity. In a word, that's what has motivated Darold Treffert, MD, throughout his career. A psychiatrist from Fond du Lac, Wisconsin, Dr Treffert today is known worldwide as a leading authority on savant syndrome. But he also has been very active around mental health rights, and writes and lectures on both along with the topic of "mellowing."



Darold Treffert, MD

"I'm a person, at least in the scientific sense, of great curiosity. When I see something I don't understand, it's intriguing to me. That's part of what got me into psychiatry," he said.

Dr Treffert said he chose psychiatry after an encounter with a patient during his internship. "One night a woman came into the emergency department. She had harmed herself and her children. She was full of self-inflicted stab wounds, blatantly psychotic and babbling. It occurred to me that I understand heart attacks a little bit, I understand asthma, but we don't have the foggiest idea really what's happening with this woman," he said. "So the field of psychiatry was of interest to me because of how little we understood. And that's the thing that triggered my interest in savants."

Dr Treffert began his career in 1962 at the Winnebago Mental Health Institute in Oshkosh, Wisconsin, where he was asked to start a children's unit. It was there that he met his first savants—4 boys who each had an extraordinary skill. One had memorized the entire bus system for the city of Milwaukee; another could put together a 500-piece jigsaw puzzle flawlessly, picture side down, based on the shape of the pieces; the third was a "walking this-day-in-history almanac;" and the fourth could make basketball free throws with amazing accuracy.

Two years later, Treffert became superintendent at Winnebago, where he spent the next 15 years. During that time, he studied savant syndrome as a hobby, examining the literature and publishing dozens of articles on the subject. "I was really intrigued by that condition," he said. "How is it possible that you can have this kind of disability and yet have these remarkable abilities?"

Then, in June 1980, Dr Treffert met Leslie Lemke, a prodigious savant with extraordinary musical talent who gave a concert in Fond du Lac. The meeting, which Dr Treffert calls "serendipitous," would literally change his life.

"A Green Bay television station taped that concert and wanted to broadcast it but they didn't really believe what they saw," Dr Treffert said. "So they brought the tapes to me as the local mental health expert and said, 'What is this and how do you explain it?' I said, 'Well I know what it is; I'm not sure I know how to explain it'."

The story was picked up by the wire services and aired nationally; then Walter Cronkite used it as his Christmas story. Leslie, his mother May, and Dr Treffert soon were appearing on high-profile TV shows including *Donahue*, the *Today Show*, *Geraldo*, *Joan Rivers*, and *Oprah*.

Public interest in savant syndrome continued to grow, and a few years later, in October 1983, *60 Minutes* aired a program called "Genius," featuring Lemke and two other savants—Alonzo Clemons and George Finn. Dustin Hoffman, who was watching that program and said he 'was moved to tears by Leslie,' decided then to play the savant in the movie *Rain Man*.

Because Dr Treffert also was involved with "Genius," he was asked to review the *Rain Man* script. "The executive producer called me and asked if I would look at the script. I asked 'Why?' He said, 'Well, first of all we want the film to be accurate and secondly, we want it to be sensitively done'."

There were some significant script changes; some "concocted" scenes were eliminated. "I said, 'you don't have to embellish anything; savant syndrome is spectacular in its own right. Stay with real characters'," said Dr Treffert. So everything you see in the movie—Judge Wapner at exactly 3 PM, the square root scene, and the toothpick scene—those all are based on actual individuals. The film was inspired by Kim Peek, but it's not Kim Peek's story. It's a composite savant. I think that lent credibility, and it was sensitively done."

Treffert said when it debuted in 1988, "*Rain Man* made autistic savant a household word. And actually, I think that movie has done more

Darold Treffert, MD, uses video-editing equipment in his home office in Fond du Lac, Wis. Dr Treffert, who is known worldwide as a leading expert in savant syndrome, edits video segments for lectures he gives on the topic as well as a website: www.savantsyndrome.org.

to bring autism onto the radar screen nationally. I don't know how you could have had a better public education effort than that movie."

Dr Treffert has done much throughout his career to educate the public, and medical and scientific communities about savant syndrome and other mental health issues. A past president of the Wisconsin Medical Society and chair of its Board of Directors, Dr Treffert also was an outspoken advocate for the "fifth standard," Wisconsin legislation passed in 1995 that allows for a patient who may be homicidal, suicidal, or gravely disabled to be placed in treatment before his or her situation deteriorates to imminent dangerousness.

Today, he is a founding member of the Dorothea Dix Think Tank, a group of psychiatrists around the country who are concerned about and working to reverse the criminalization of mentally ill. "There are more mentally ill people in prisons now than in the hospital, which is a just a tragedy," Dr Treffert said.

Still, most of Dr Treffert's work focuses on savant syndrome. He has published two books: *Extraordinary People: Understanding Savant Syndrome* in 1989 and *Islands of Genius: The Bountiful Mind of the Autistic, Acquired and Sudden Savant* in 2010. Now in its third printing, *Extraordinary People* was updated most recently in 2006 and is available in 10 languages. *Islands of Genius* was published in 2010 and won a gold medal in the Psychology and Mental Health category of the 2011 Independent Publisher Book Awards. It provides an update on well-known savants Dr Treffert has followed for years and explores new cases, particularly the "acquired savant" in which neurotypical persons demonstrate previously dormant savant skills, sometimes at a prodigious level following head injury or central nervous system disease. It also explores genetic memory—how savants "know things they never learned."

"What started out as kind of a hobby is really full-time," said Dr Treffert. Following his tenure as superintendent at the Winnebago Mental Health Institute, Treffert spent the next 12 years dividing his time between private practice and as director of the Fond du Lac County Mental Health Center. He "retired" in 1991, and today continues to research, lecture, and write, including a recent manuscript on hyperlexia published in the December 2011 issue of *WMJ*. And although he works out of an office in his home, the audience for his work is truly global.

Not long after "Genius" aired in 1983, the Driscol Gallery in Denver hosted the world premier of the artwork of Alonzo Clemons, one of the savants featured in the show. The gallery expressed an interest in donating some of the proceeds from the show to a charity or foundation to further research and education about savant syndrome. From that, the Clearinghouse for Information Regarding Savant Syndrome was established at the Wisconsin Medical Society Foundation. Years later, in 1997, the clearinghouse added a website, www.savantsyndrome.org, which is hosted by the Wisconsin Medical Society. The site features a plethora of information about savant syndrome, including profiles, videos, articles, and answers to frequently asked questions.

"The website has just been a gold mine of opportunity for communication both

ways. I get in touch with people or they get in touch with me. I continue to be amazed at the breadth and scope of the site," said Dr Treffert, who added that the inquiries he receives generally fall into 1 of 4 categories:

- requests from reporters and documentary producers
- students, ranging from fourth graders through PhD candidates, working on papers
- scientific inquiries from other clinicians doing research, looking for references, and networking
- parents or clinicians describing a son or daughter or patient and asking if they might be a savant, and if so, how to proceed

A recent 2-week sampling included media inquiries from CBS New York, magazines from France and Ecuador, and *60 Minutes* Australia; a student in Stockholm, Switzerland; the mother of a savant; 2 parents of hyperlexic children; and a request from UCLA to review a manuscript.

"One of the offshoots of these inquiries is that a number of people write to me and tell me that they want to go into neuroscience," Dr Treffert said. "That provides a great deal of satisfaction for me because I'm recruiting 'fresh new explorers'."

Contacts through the website also have connected Dr Treffert to many "new" savants and have fueled his desire to develop a savant registry. Last summer, through a grant from the Wisconsin Medical Society Foundation, medical student David Rebedew worked with Dr Treffert to create the registry. Currently, it documents 309 savants from 33 countries, ranging from those with splinter skills to prodigious savants. It also separates congenital savants from acquired savants. Once registered, additional, standardized information is gathered from each savant or caregiver, including underlying disability, most common skill, gender, and ethnicity.

Dr Treffert's long-range goal is to establish a savant institute to encourage multidisciplinary research and house the work that's already been done.

"One of the things that has been so impressive to me is not just how little we know about the brain, but how marvelous and how intricate and how extraordinary the brain is," said Dr Treffert. "I simply have become more enamored, more fascinated, and more impressed with the brain. That keeps me going."

For Dr Treffert, it's not just about the science behind savant syndrome, though. It's about the people.

"It's very gratifying. I've had the opportunity to meet many savants and their families. They're just delightful people, and we've gotten to be good friends," he said.

Perhaps his greatest satisfaction, however, lies in the future. When recounting a presentation to a fourth-grade class, Dr Treffert said, "At the end, a boy and a girl came up, and the boy said, 'I want to be a scientist, and I want to do what you do,' and the girl said, 'me too.' I thought the day they walk across the stage and get their degree in neuroscience, that will be the pay-off."

A Potpourri

John J. Frey, III, MD, *WMJ* Medical Editor

Case reports still constitute a large contribution to the biomedical literature. Most of the syndromes, diagnoses, clinical findings, and a great deal of the understanding of chronic diseases started out being single or multiple case reports. All of the eponymous anatomical and clinical points that many of us learned in training and had to substitute with more descriptive terms (Parkinson's syndrome is easier to remember and easier to visualize than paralysis agitans) started with descriptive case studies in journals or books. Biomedical journals such as *The New England Journal of Medicine, JAMA*, and many longtime specialty journals had very few "research" articles until the early 1960s. So there is a long tradition of case reports in the literature.

The 3 examples in this issue present unusual stories—clinical stories—that start with a puzzling presentation, a workup that may lead down blind alleys and eventually come upon a diagnosis that clarifies what treatment to use or what prognosis to give. Whether it is an elderly man becoming confused and agitated who appears to have neuroleptic malignant syndrome and turns out to have rabies,[1] or a teenager who is brought to an emergency department with severe symptoms of a stroke and documentation of multiple pulmonary emboli emanating, it turns out, from venous thromboembolism through a patent foramen ovale,[2] or a middle-aged man with a complicated course of a disease that keeps his doctors guessing about the etiology for 2 years,[3] the case reports in this issue enlighten us about the complexity of unusual disease or complex presentations of common diseases.

Two articles raise important policy issues for the practicing community and for the health systems in which many of us work. Mindock and colleagues[4] found a strong belief in the value of involuntary commitment of patients for alcohol dependence from public health and elected officials of the counties in Wisconsin, but a wide range in the use of that law to treat patients. While physicians are not required to be a part of the commitment process, they have great influence over family members who are often desperate to find an approach to chronic relapsing alcohol dependency. In studies over the past 40 years, alcohol continues to be second only to tobacco as a contributor to all-cause mortality with a particular prevalence in the upper Midwest. If funding for involuntary treatment is required—and municipalities have to contribute to part of the cost—then we need to avoid the penny wise, pound foolish approach to a health problem that costs us far more not to treat. And physicians need to lead.

Finally, the interaction between required and voluntary when it comes to public health issues has been a source of debate and discussion over the 106 years of publication of the *WMJ*. "Freedom to choose" vs the common good is an inherent source of conflict in this country, even echoed in the recent Supreme Court discussion about the Affordable Care Act. The article by Smith and Van Cleave[5] shows how a requirement for influenza vaccination for employees of one of the largest non-federal health systems in the country has accomplished almost universal coverage, which will decrease the likelihood of transmission in the workplace and should decrease the loss of work time and illness in employees. The debate over children's vaccine often misses the fact that required vaccine for school attendance changed everything over the past 20 years. Health policy based on evidence and common sense (which unfortunately does not insure that people will agree with them) such as smoking in the workplace, immunizations for school attendance, TB testing, and Hepatitis B immunization for health care workers has changed societal risks for the better over the past 50 years. Employers requiring influenza vaccine as a condition of employment simply adds to that positive record in an era where widespread concern about the potential for epidemic influenza is quite real.

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Prevalence of Involuntary Commitment for Alcohol Dependence

Susan Mindock, LPC, CSAC; Katherine Wright, MPH; Michael F. Fleming, MD, MPH

ABSTRACT

Background: Alcohol dependence is a chronic relapsing illness. While some patients respond to treatment, others continue to drink alcohol and suffer serious health effects such as delirium tremens, liver failure, heart disease, and central nervous effects. One option society has used to force treatment and abstinence is the legal mechanism of "involuntary commitment." The goal of this study was to determine the utilization of "involuntary commitment" among the 72 counties in Wisconsin.

Methods: A statewide survey was conducted using a mailed survey to assess the current use of this treatment option.

Results: Forty-nine counties responded to the survey (68%); the mean number of commitments in the last year was 5 with a range of 0 to 30. Of the petitioners who participated in the commitment, 98% were family members, 62% were friends, 49% were physicians, and 26% were counselors. Over half of the respondents (53%) felt that the process was effective in helping people deal with their alcoholism.

Discussion: The overall perception among those surveyed is that involuntary commitment for the treatment of alcohol dependence can help addicted persons, but its utilization varies by county in Wisconsin. Physicians may consider exploring the use of this legal process to assist patients struggling with alcoholism.

INTRODUCTION

The aim of this article is to provide a statewide snapshot of involuntary commitment (IC) for alcohol dependence. In 1968 congress passed the Alcoholic Rehabilitation Act of 1968 (Public Law 90-574), which was the first federal law to address the need for alcoholism to be treated as a health problem vs a criminal problem. By 1971 this legislation was expanded to The Uniform Alcoholism and Intoxication Treatment Act, which allowed states to provide the health and legal guidelines to treat alcoholism.[1] Following this federal act, the state of Wisconsin enacted legislation that addressed the issue of involuntary commitment for alcoholism. This state statute defines an involuntary alcohol commitment as "a civil, legal proceeding which allows for an alcohol or drug dependent individual who is dangerous as a result of that use, to be placed in a treatment setting against his/her will."[2] Other states have enacted similar statutes.

The commitment process in Wisconsin requires 3 adults to sign sworn petitions for examination alleging concern that the individual is a danger to self or others and is a proper subject for treatment. A probable cause hearing occurs within 72 hours and the judge determines the outcome. If probable cause is found, a final hearing will occur and the treatment course determined. Prior to the final hearing, which may take a few days, the person may remain in the medical facility, a detoxification facility, a shelter, or at home. A common outcome is treatment in a residential or outpatient alcohol treatment program for a period of 30 to 90 days.

Involuntary commitment and court-ordered treatment policies are supported by The National Alliance on Mental Illness (NAMI) for persons with mental illness.[3] Historically, involuntary commitment is used less commonly to treat alcohol use disorder (AUD) than for mental health purposes, and usually has separate implementation criteria.

Alcohol abuse is a prominent public health concern in Wisconsin. The state leads the country in rates of current alcohol use, heavy use, and binge drinking among adults.[4] In addition, alcohol-related injuries and diseases account for a significant number of emergency department (ED) and primary care visits.[5] Previous research has estimated that problem drinkers are twice as likely to report ED use compared to non-problem drinkers, even when controlling for other factors such as gender, age, and insurance status.[6] Physicians often face the

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Table. Sample Survey Questions

Does your county execute three-party involuntary alcohol commitments?
Is there a waiting list? If yes, how long, and is there a limit of commitments per individual?
Describe the commitment process. Who are the typical petitioners? Who oversees the process in your county? Is it the same individual for each commitment?
Does your county track commitments? Has there been a change in numbers in the last 5 years? 10 years?
What has affected the numbers of commitments done in your county?
Where do individuals seek treatment for their commitments?
Is follow-up data collected?
How much money is spent per year on commitments?
Do you think commitments are effective?

dilemma of how to manage patients who do not respond to other methods of treatment and may harm themselves or others as a result of their alcohol or drug use disorder.

Because state and federal regulations are different, the commitment process varies throughout the country, and from county to county in Wisconsin. This article presents the results of a statewide survey of county corporation counsel or health and human service departments in order to provide clinicians with a better understanding of the alcohol commitment process by county.

METHODS

Representatives from either the health and human services department or county corporation counsel's office in each of Wisconsin's 72 counties were contacted to participate in the study during August and September 2010. Each representative was identified as the primary contact regarding involuntary alcohol commitments in their county via a telephone conversation with their county health and human services agency. Approval for this project was obtained through the University of Wisconsin-Madison Health Sciences Institutional Review Board. The analysis was completed by research staff at the University of Wisconsin.

A survey instrument was designed to gain understanding of the alcohol commitment process and trends in Wisconsin counties. The estimated time to complete the survey was 10 minutes. This survey was mailed to the identified representative of each county. If no response was received within 2 to 3 weeks of the initial mailing, a follow-up telephone call was placed prompting them to return the survey. Completed surveys were used as the data source. The survey questions included both preselected options and open-ended questions. (See Table)

The survey questions provided factual information regarding whether or not a county executed involuntary alcohol commitments, data collection, and number trends. The survey also provided an opportunity for the county representative to expound on their clinical impressions regarding the effectiveness of such commitments and what may have affected the number of commitments done. The survey was returned by 49 of the 72 counties (68%). Descriptive analysis was completed using SPSS. The data did not lend itself to statistical testing or differences by county.

RESULTS

Of the 49 county representatives who returned the survey, 44 representatives reported that their county currently utilized 3-party involuntary alcohol commitments to help county residents deal with their alcoholism. The number of commitments ranged from 0 to 30 in a typical year, with 12 (25%) counties reporting no IC in 2010. The remaining 37 (75%) counties reported an average of 5 commitments per year. When asked if there was a waiting list and how long a person would have to wait to be committed, 75% (n = 37) reported a waiting time of up to 3 months.

According to the survey, a majority of the petitioners for alcohol commitments are family members (97.73%), followed by friends (66%), physicians (50%), and social workers or counselors (25%). A majority of these commitments are overseen at the county level by the county human and social services agencies (72.72%), followed by corporation counsel (48.8%), and a mix of other agencies such as alcohol and other drug abuse (AODA) treatment centers, case management agencies, mental health coordinators, or unified community services. A majority of the treatment for commitment is sought either at inpatient or outpatient facilities (90.90%), followed by in-county facilities (79.55%) and out-of-county facilities (77.27%).

The survey also inquired about changes in number of commitments and some of the possible reasons that could have affected alcohol commitments. Of the total number of counties who answered the survey, 23 (48%) reported that the number of commitments remained the same over the last 5 years, and approximately one-third reported a decrease in the number of commitments.

Some of the possible factors reported by respondents to have affected the number of commitments were budget cuts (11.36%), decreasing number of referrals (11.36%), physicians unwilling to testify to successfully complete a commitment (11.36%), lack of alcohol and drug treatment facilities (9.09%), lack of resources (9.09%), a belief that commitments are ineffective (6.8%), and lack of family and community understanding about referrals (6.8%).

Finally, when questioned on budgets and the effectiveness of commitments, 68.18% of respondents reported that they did not have a separate budget for involuntary commitments.

Slightly more than half of the county representatives believed that commitments are effective (52.27%).

DISCUSSION

This paper presents new information on the utilization of involuntary commitment for alcohol dependence in Wisconsin. The report suggests that the use of this mechanism varies by county. Family members are the primary petitioners. These families try to work with local courts to obtain treatment for loved ones suffering from alcoholism. There is the overall perception that this legal option can help addicted persons, their family members, and friends to deal with alcoholism.

Why would a physician choose this option to help their patients? First, some patients are so resistant to any kind of help that forced sobriety over a 3-month period may provide sufficient healing of brain pathways to initiate long-term recovery. Second, while there is no primary outcome research on efficacy, anecdotal experience by the authors suggests involuntary commitment may prolong life and reduce the frequency of detoxification admissions, repeat admissions for acute pancreatitis and other medical sequelae of alcoholism. Third, it can provide resources for treatment that are otherwise not available. County funding for 90 days of treatment often is available to people with alcohol dependence who have limited resources to pay for alcohol treatment.

Physicians struggle with patients who have chronic relapsing alcoholism. There are no easy answers. However, unlike most brain diseases, the effects of alcoholism on the brain are at least partially reversible. Long-term recovery is possible, with many recovering alcoholics leading productive and accomplished lives. While many physicians are not comfortable with some of the methods used to get people into treatment, involuntary commitment is another recovery tool available to physicians and families. Physicians who are not familiar with procedures in their county may want to contact the local county board, the county judge, or county mental health center for more information.

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A Case of Pulmonary Embolism and Stroke in a 16-year-old Girl

Sujana Gunta, MD, MS; Sameer Kamath, MD

ABSTRACT

A 16-year-old girl arrived intubated to the emergency department. She had shortness of breath and cough for 2 days with leg pain. On arrival, she was hemodynamically stable with an unremarkable physical exam. Electrocardiogram revealed a prolonged QT interval; laboratory work-up was normal except for an elevated dimerized plasmin fragment D. Acute pulmonary embolism was confirmed by a chest computed tomography scan. A lower extremity duplex scan was negative and echocardiogram revealed a patent foramen ovale with bidirectional shunting. An inferior vena cava filter was placed to prevent acute recurrence and unfractionated heparin was initiated. The next day she was noted to have right hemiparesis. Stroke was confirmed by magnetic resonance imaging. The patient underwent mechanical clot retrieval and was discharged on anticoagulation therapy to a brain rehabilitation unit.

INTRODUCTION

Patent foramen ovale has been implicated in cryptogenic strokes in adults.[1] There is increasing pediatric data on cryptogenic strokes, where paradoxical emboli are presumed to be the cause of stroke.[2] Although adult cases of pulmonary embolism and stroke in the presence of a patent foramen ovale have been described,[3] our search revealed no such pediatric cases. Here, we present the case of a previously healthy adolescent female with pulmonary embolism and stroke in the presence of a patent foramen ovale.

CASE DESCRIPTION

A 16-year-old girl was found at home by family members, unresponsive and with labored respirations. Emergency medical service personnel noted spontaneous respirations, stable vital parameters and a Glasgow Coma Scale (GCS) of 6. She arrived intubated to the emergency department in sinus tachycardia, with stable blood pressure, adequate perfusion, and normal oxygen saturation on minimal ventilator settings. She had been hiking with family members the preceding week and had arrived home after a long car ride the previous day. She had developed some cough and shortness of breath 2 days before admission. Her past medical and social history was unremarkable. She had been initiated on oral contraceptive pills 4 to 5 months before. Her family history was significant for venous thromboses and pulmonary embolism in the maternal grandfather. Laboratory work-up was normal except for an elevated dimerized plasmin fragment D (D-dimer) level of 13.42 mcg/ml (normal: <0.5 mcg/ml). Electrocardiogram (ECG) revealed sinus tachycardia with prolonged QTc (500 ms). Head and neck computed tomography (CT) scans were normal. The patient was transferred to the pediatric intensive care unit for further care following a chest CT scan.

Cardiopulmonary, abdominal, and musculoskeletal exams were unremarkable. She was withdrawing all extremities to painful stimuli and no obvious asymmetry was noted on neurological exam. Remifentanil infusion was used for sedation to allow frequent neurological assessments. ECG continued to show prolonged QTc (480 ms) without any other abnormalities. Chest CT scan revealed massive bilateral pulmonary embolism (Figure 1). Duplex study of the lower extremities was negative for any thromboses. Unfractionated heparin therapy was initiated and appropriate consults were obtained. Given the size of the pulmonary emboli, a retrievable inferior vena cava (IVC) filter was placed to prevent any further pulmonary embolism. The patient was switched to enoxaparin (low molecular weight heparin) for continued anticoagulation after the filter placement. Echocardiogram revealed right ventricular dilatation with normal left ventricular function and a patent foramen ovale with bidirectional shunting. No asymmetry had been noted on the patient's exam until shortly after extubation

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when she was noted to have right-sided hemiparesis and aphasia. A head CT scan and magnetic resonance imaging (MRI) obtained thereafter showed a new left striatocapsular and internal capsule infarct in M1 distribution with no acute bleeds (Figure 2). A conventional cerebral arteriogram confirmed occlusion of the left mid-M1 segment and proximal M2 segment of the middle cerebral artery with minimal distal filling suggesting thrombotic occlusion. The thrombus was retrieved with a penumbra device with improvement in hemiparesis and aspirin initiated shortly after mechanical clot retrieval.

The patient was tested for prothrombin and methylenetetrahydrofolate reductase (MTHFR) gene mutation, factor V Leiden and antiphospholipid syndrome. She was noted to be homozygous for MTHFR mutation with homocysteine level in the normal range. Enoxaparin and aspirin were continued at discharge. She underwent brain rehabilitation with marked improvement in function.

Protein C, protein S, and antithrombin III (ATIII) levels obtained at a follow-up visit showed ATIII deficiency. Anticoagulation therapy was switched to warfarin and the patient was counseled against the use of oral contraceptives. She was scheduled for filter retrieval with a plan to close the patent foramen ovale at a later date.

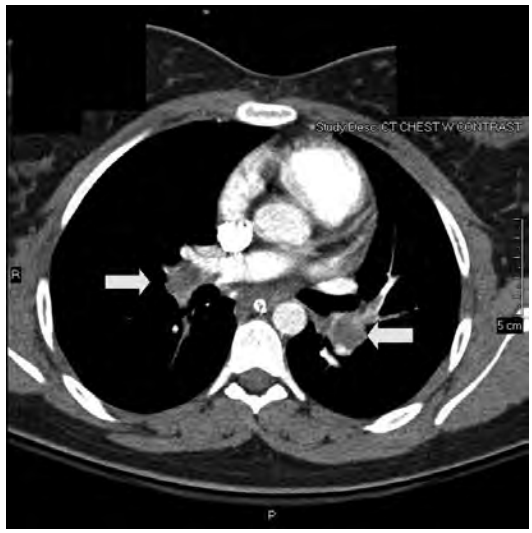

Figure 1: Chest CT Scan Showing Bilateral Pulmonary Embolism

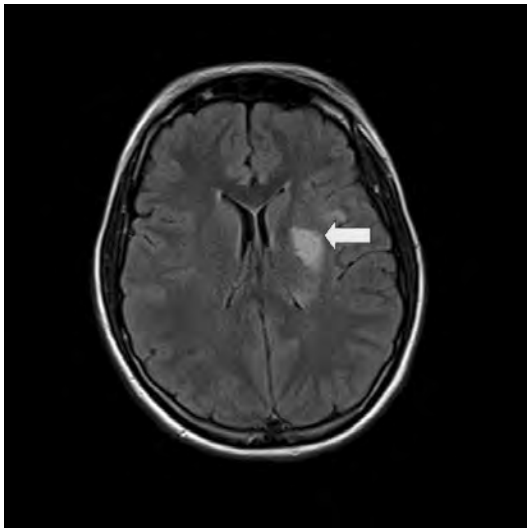

Figure 2: Brain MRI Showing Left Striatocapsular and Internal Capsule Infarct

DISCUSSION

We believe our case to be the first pediatric case report of a documented stroke and pulmonary embolism in the presence of a patent foramen ovale.

Our patient was taking oral contraceptive pills and had recently traveled long distances in a car. Contraceptive pills are a known risk factor for venous thromboembolism, especially for women in the reproductive age group. She had been complaining of leg pain and shortness of breath prior to the sudden syncopal event, suggesting the possibility of venous thromboses and pulmonary embolism. The term "economy class syndrome" was coined in 1988 to describe the association between prolonged travel and thrombosis. The initial articles implicated prolonged air travel; however, recent articles suggest that prolonged bus and car rides also may contribute to the development of thrombosis.[4]

The presence of a prolonged QTc in pulmonary embolism is described, but is infrequent and not specific to this diagnosis.[5] Our patient's QTc interval normalized on day 2, thus lowering suspicion for prolonged QT syndrome.

A lower extremity Doppler ultrasound test was negative for any thromboses; upper extremity Doppler was not performed. Duplex scanning has a sensitivity of 100% and specificity of 98% for proximal symptomatic deep vein thrombosis, and 94% sensitivity and 75% specificity for distal symptomatic deep vein thrombosis. However, its sensitivity is controversial in asymptomatic patients.[6] Doppler studies tend to be operator dependent and some experts believe that a negative study does not rule out venous thromboses.

An echocardiogram revealed a patent foramen ovale with bidirectional shunting in our patient. Prior to this admission, the patient had never had an echocardiogram. The statistical association of a patent foramen ovale with stroke in children has been shown, but a causal relation has been difficult to establish in pediatric cryptogenic strokes.[2] The prevalence of a patent

foramen ovale in the general population is 10% to 25% and the prevalence in patients with stroke is in the range of 40% to 45%.[7] Currently, there are no FDA-approved indications for foramen closure in the United States. There is evidence for a decrease in recurrent strokes with foramen closure, and current practice consensus in the United States is its closure in these cases.[8] With growing data on safety of the closure devices, a single event might justify placing one in such patients.

The standard of care for venous thromboembolism is systemic anticoagulation alone. IVC filter placement is indicated only in patients who cannot receive anticoagulation. Filter placement may be justified in cases of pulmonary embolism where an acute recurrence can prove life-threatening.[9] There were no known contraindications to anticoagulation in our patient, and unfractionated heparin was initiated as soon as the diagnosis of pulmonary embolism was made. We elected to place the filter to prevent any acute recurrences.

There is early clinical experience with the Penumbra System (Penumbra, Inc USA, Alameda, Calif) for mechanical clot retrieval. It is indicated in large vessel occlusion and has a high recanalization rate. The safety of the procedure increasingly is being established with decreased incidence of symptomatic hemorrhage.[10] Our patient underwent clot retrieval as soon as the diagnosis of stroke was made and the thrombus identified. She tolerated the procedure well and had partial recovery of neurological function immediately after the procedure. It is difficult to comment on the timing of her stroke. Frequent neurochecks had not revealed any obvious asymmetry prior to extubation. Neurological assessment in sedated and mechanically ventilated patients tends to be limited and we may have missed an earlier diagnosis of stroke.

Anticoagulation management was based on American College of Chest Physicians guidelines for management of venous thrombosis and pulmonary embolism. Aspirin was initiated after the stroke was diagnosed. A decision for lifelong anticoagulation treatment was made on follow-up when the patient was noted to be homozygous for the C677T genetic variant of MTHFR and ATIII deficient. This genetic variant of MTHFR is a known risk factor for thrombosis. Patients with hypercoagulability have a higher incidence of pulmonary embolism and paradoxical embolism in the presence of a patent foramen ovale.

CONCLUSION

Venous thromboembolism is underappreciated in pediatrics, and the diagnosis is not considered very often by pediatric health care providers. Oral contraceptive pills are known to precipitate venous thromboembolism. Other risk factors for thrombosis, such as prolonged travel, smoking, and family history of venous thromboembolism should be explored prior to prescribing oral contraceptive pills. If a family history for venous thrombosis exists, testing for known hypercoagulable states or a hematology consult should be considered. Families of patients receiving oral contraceptives should be counseled about the possible signs and symptoms of venous thromboembolism so that they can seek timely medical attention if symptoms appear. Differential diagnoses of a syncopal event in an adolescent could include pulmonary embolism in the appropriate setting.

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Pulmonary Lymphomatoid Granulomatosis Presenting with Neuropathy and Renal Nodules

Vikas Pathak, MD; Govinda Aryal, MD; Lawrence H. Clouse, MD

ABSTRACT

Pulmonary lymphomatoid granulomatosis is a rare diagnosis that frequently presents with a constellation of seemingly unrelated signs and symptoms. It can present with bilateral pulmonary nodules, subcutaneous skin nodules, renal nodules, and peripheral neuropathy. Its protean manifestation, both clinically and radiologically, may delay a definitive diagnosis. We present the case of a patient who had thoracotomy twice and waited for nearly a year to get the final diagnosis because of the presence of a variety of seemingly unrelated symptoms.

CASE PRESENTATION

A 55-year-old man presented with a 4-week history of bilateral chest wall pain. He denied any history of cough, fever, dyspnea, hoarseness, diaphoresis, rash, recent chest trauma, or exposure to respiratory illnesses. He had no pre-existing lung disease and was taking no medications. He smoked a half-pack of cigarettes per day for 30 years, had no history of alcohol or drug abuse, and no contributory family history.

Physical examination and laboratory studies (including complete blood count and complete metabolic panel) were normal. Rib views were normal, but a chest radiograph suggested an abnormality in the left lower lobe. Computed tomography scan (CT) of the chest demonstrated a 2.5 cm mass adjacent to the left diaphragm with small satellite nodules (Figure 1A). Pulmonary function testing showed borderline restriction with total lung capacity and vital capacity both around 80% predicted. The mass was resected via thoracotomy, with pathologic material described as "lymphoplasmacytic and noncaseating granulomatous pneumonitis with atypical lymphoid infiltrate." It did not meet criteria for B-cell lymphoma, as there were few B-cells in the infiltrate and plasma cells were not light chain restricted. There was no definite diagnosis.

The patient continued to have painful chest wall neuropathy requiring gabapentin and opioids. Magnetic resonance imaging (MRI) of the thoracic spine and brain were normal. A repeat chest CT 4 months later showed postoperative changes and a possible new small (< 1 cm) contralateral lower lobe pulmonary nodule adjacent to the pleura.

The patient was referred to neuro-oncology. A lumbar puncture and paraneoplastic antibody panel were normal. Electromyogram and nerve conduction studies demonstrated axonal polyradiculoneuropathy. Although there was no significant demyelination, the pattern was suggestive of chronic inflammatory demyelinating polyneuropathy. He was started on prednisone and intravenous immune globulin. The painful chest wall neuropathy improved but did not resolve completely.

One year later, the patient presented with right flank pain. A chest CT showed innumerable bilateral lung nodules and masses in a lower lobe predominant pattern. Some were round, but many were irregular. (Figure 1B). The CT also showed peculiar kidney mottling. Pulmonary function testing showed a mild restrictive pattern with FEV1/FVC, total lung capacity, and diffusing capacity of the lung for carbon monoxide all 70% to 73% predicted. Open lung biopsy was repeated on the right lung.

Histopathological slides revealed blood vessel injury accompanied by nodules of lymphocytes and plasma cells with relatively large areas of necrosis. Capillaritis was not detected. Necrosis was ischemic in appearance rather than coagulative. Histiocytes and giant cells were present, but were relatively

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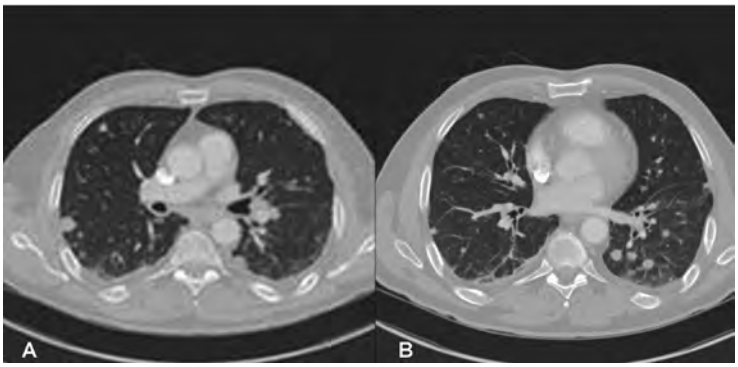

Figure 1: Chest CT demonstrating (A) a 2.5 cm mass adjacent to the left diaphragm with small satellite nodules; (B) innumerable bilateral lung nodules and masses in a lower lobe predominant pattern.

rare. There was sclerosis and obliteration of veins and arteries. Rather than vasculitis, the lesion was an angiocentric B-cell lymphoma.

DNA was extracted from the tissue for B-cell gene rearrangement studies by polymerase chain reaction (PCR). Reactions for Framework 3, Kappa 1, and Kappa 2 all showed a clonal pattern, consistent with the morphologic diagnosis of lymphoma. Immunochemical staining showed Epstein-Barr virus (EBV) involvement of scattered B-cells (Figure 2). Based on histopathological examination of the biopsy, the patient was diagnosed with having pulmonary lymphomatoid granulomatosis (EBV-positive diffuse large B-cell lymphoma).

Subsequent staging included a normal head CT (we were unable to do a brain MRI due to recent metallic clips in his chest), a positron emission tomography (PET)/CT scan that showed many of the nodules had only moderate FdG glucose SUV intensity 2.7 to 6.8 (many of the nodules were FdG-negative), and a normal resting cardiac ejection fraction of 74%. The patient declined a bone marrow biopsy. A vascular port was placed, and he was started on chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Marked improvement was noted on a PET/CT scan after 2 cycles of treatment.

DISCUSSION

First described as a clinicopathologic entity by Averill Liebow and colleagues in 1972,[1] pulmonary lymphomatoid granulomatosis (PLG) is an uncommon multi-organ systemic disease with a predilection for the lungs, characterized by multiple pulmonary nodular lesions with lymphocytic invasion of vascular walls on biopsy. The World Health Organization classification scheme places lymphomatoid granulomatosis under the generic heading of B-cell proliferations of uncertain malignant potential.[2] Lymphomatoid granulomatosis is generally considered a B-cell lymphoma with an associated exuberant, benign T-cell reaction. It is described as an extranodal, angiocentric, T-cell rich, B-cell lymphoma. The prominent T-cell component is polyclonal and reactive.

The pathogenesis of lymphomatoid granulomatosis is unknown. These lymphoproliferative disorders are in the family of EBV-associated B-cell lymphomas.[2] Recent studies using a combination of PCR and in situ hybridization show that most lymphomatoid granulomatosis cases have malignant B-cells containing EBV RNA. EBV infection causes continuous growth of infected B-cells. When carefully evaluated clinically, most patients with PLG have defects in cytotoxic T-cell function and reduced levels of CD8+ T-cells; this leads to unchecked growth as immune responses cannot stop this growth.[3] In addition, PLG can be seen in patients with an underlying immunodeficiency such as AIDS, Wiskott-Aldrich syndrome, and post-transplantation immunodeficiency or other lymphoproliferative disorder.[4,5] In immunodeficient states, the host's defenses are unable to curb EBV-induced B-cell proliferation. These immune defects may lead to an abnormal host response to EBV infection, resulting in lymphomatoid granulomatosis rather than clearance of the viral infection.[3] PLG has been reported in patients being treated with azathioprine and methotrexate,[6,7] implying defective immune response in clearing EBV-infected cells.

Although PLG can affect patients at any age, the incidence peaks in the 30 to 50 year age range. It is seen predominantly in men, with an estimated male to female ratio of at least 2:1.2 The lung is the most commonly involved organ (> 90%),[2] while the skin (50%), kidney (32%), and neurologic system (30%) may be affected concurrently or independently.[2,4] The liver, lymph nodes, spleen, and bone marrow usually are spared until late in the course of the illness.[2] Cough (60%) and dyspnea (30%) are the most common presenting symptoms in patients with lung involvement. Patchy, occasionally painful, erythematous macules, papules, and plaques typically involve the gluteal regions and extremities.[8] Extensive lymphocytic infiltration of the meninges, cerebral vessels, and peripheral nerves is found in as many as 25% of patients. Peripheral nerve involvement may include distal sensory neuropathy or mononeuritis multiplex.

Systemic presentation of lymphoma-related B symptoms in patients include fever (60%), weight loss (35%), and malaise (35%).[3] Rarely, patients may be asymptomatic.

Generally, physical examination of the lungs is normal and laboratory studies are nondiagnostic. No characteristic pulmonary function test abnormalities have been reported.[9] Chest radiography typically reveals multiple poorly defined nodules and/or masses in the mid- and lower-lung zones. Diffuse reticular abnormalities also may be present.[2,5] Chest CT usually shows both well-defined and poorly-defined nodules throughout both lungs. Most lesions are less than 1 cm in diameter, but larger cavitary masses have been reported.[10,11] The EBV-positive B-cells typically express CD20 and may express CD30. The background lymphocytes are CD3-positive T-cells which more often express CD4 than CD8.[2]

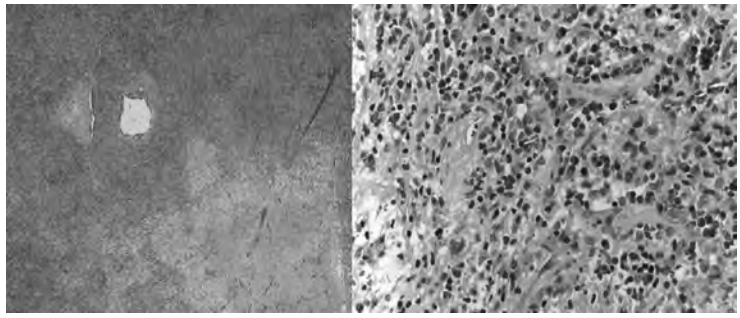

Figure 2: (A) Histopathology slide showing lung tissue with necrosis and a cellular infiltrate that completely obliterates normal lung tissue (40 x magnification); (B) Higher magnification (400 x) shows that the infiltrate is composed of small lymphocytes, fibroblasts, plasma cells, and large atypical cells with folded and irregular nuclei. These large atypical cells are neoplastic B-lymphocytes as demonstrated by immunohistochemical and gene rearrangement studies.

A definitive diagnosis of lymphomatoid granulomatosis requires the presence of the following histological triad: polymorphic lymphocytic infiltrate (nodular polymorphic lymphoid infiltrate composed of small lymphocytes, plasma cells, and variable numbers of large atypical mononuclear cells); angiitis due to transmural infiltration of arteries and veins by lymphocytes (a process distinct from vasculitis in which acute and chronic inflammatory cells are found with associated vessel wall necrosis); and granulomatosis (central necrosis within the lymphoid nodules and not granuloma formation).

The therapeutic approach and optimal management have not been well-defined. In several studies, therapy has ranged from observation to treatment with chemotherapy.[3,5,8,11] Patients with PLG are treated as diffuse large B-cell lymphoma (DLBCL, which includes 4 chemotherapeutic agents including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Rituximab, a monoclonal antibody directed to the CD20 antigen on B-cell lymphoma cells, also has been used. The addition of rituximab therapy has shown to improve outcomes in these patients.[12] Interferon-alpha2b is the other agent that has been used successfully to induce remission in PLG. There have been some case reports and case series that have demonstrated improved clinical outcomes following treatment with interferon-alpha 2b.[13-15]

The prognosis for PLG is variable. Katzenstein et a[l4] reported on a clinicopathologic study of 152 cases who were thought to have PLG. Ninety-four of 148 patients with complete follow-up data (63.5%) died. The median survival was 14 months. Patients less than age 25 years, those with neurologic involvement, and those having hepatosplenomegaly, had worse outcomes; while asymptomatic patients and patients with unilateral lesions had more favorable outcomes. Approximately 20% of patients achieved clinical remission without treatment.

CONCLUSION

In patients presenting with pulmonary nodules, peripheral neuropathy and renal nodules, PLG should be considered in the differential diagnosis. PLG is a form of lymphoproliferative disorder, and it can be seen in patients with an underlying immunodeficiency. The histological triad of polymorphic lymphocytic infiltrate, angiitis, and granulomatosis is necessary for diagnosis.

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CME

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Quiz: Pulmonary Lymphomatoid Granulomatosis Presenting with Neuropathy and Renal Nodules

EDUCATIONAL OBJECTIVES

1. To be able to describe the major clinical and laboratory features for a patient presenting with pulmonary lymphomatoid granulomatosis (PLG).
2. To be able to describe the pathologic features diagnostic of PLG.
3. To be able to describe the usual course and treatment for PLG.

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QUESTIONS

1. Pulmonary lymphomatoid granulomatosis (PLG):
   - ❑ a. is a multi-organ systemic disease that usually affects the lungs with a lymphocytic invasion of vascular walls on biopsy
   - ❑ b. is generally considered a B-cell lymphoma.
   - ❑ c. has a benign, reactive T-cell component
   - ❑ d. a and b only
   - ❑ e. all of the above

2. Most cases of PLG:
   - ❑ a. are seen in patients with an underlying immunodeficiency disorder such as AIDS
   - ❑ b. are associated with malignant B-cells containing Epstein-Barr Virus RNA
   - ❑ c. have defects in cytotoxic T-cell function
   - ❑ d. a and b only
   - ❑ e. all of the above.

• • •

3. Clinical manifestations of PLG usually include:
   - ❑ a. lung nodules, often greater than 1 cm in diameter, in more than 90% of patients
   - ❑ b. skin involvement with patchy erythematous macules, papules, and plaques in about half the patients
   - ❑ c. early involvement of the liver and spleen in a majority of cases
   - ❑ d. a and b only
   - ❑ e. all of the above

4. Which of the following statements is false?
   - ❑ a. The definitive diagnosis of lymphomatoid granulomatosis on biopsy requires the presence of a polymorphic lymphocytic infiltrate, angitis due to transmural infiltrate of arteries and veins by lymphocytes, and granulomatosis with central necrosis within the lymphoid nodule.
   - ❑ b. Patients with PLG are treated as diffuse large B-cell lymphoma.
   - ❑ c. Most patients have a benign course with a 5-year survival of over 80%.
   - ❑ d. Patients under age 25, those with hepatosplenomegaly, and those with neurologic involvement had worse outcomes.
   - ❑ e. About 20% may achieve a clinical remission without treatment.

You may earn CME credit by reading the designated article in this issue and successfully completing the quiz (75% correct). Return completed quiz to *WMJ* CME, 330 E Lakeside St, Madison, WI 53715 or fax to 608.442.3802. You must include your name, address, telephone number, and e-mail address.

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An Acute, Progressive Encephalopathy

Ernesto Brauer, MD; John C. O'Horo, MD

ABSTRACT

Rabies holds the distinction of having the highest case-fatality ratio of any infectious disease. Aggressive public health campaigns have reduced the incidence of this disease in the United States to a record low. We report a case of this increasingly rare disease in a 70-year-old man in Wisconsin.

CASE PRESENTATION

A 70-year-old man with a past medical history significant for alcoholism (>7 drinks/day) was admitted to a community hospital for altered mental status of 2 days' duration. His confused state had been worsening, and his continuing deterioration led his wife to bring him to the emergency department. While there, the patient became increasingly agitated. Lorazepam and haloperidol were administered, but the patient became more irritable and began to have muscle spasms. He was admitted and evaluated by neurology; initial CT was negative for acute abnormality and the patient was treated for severe alcohol withdrawal. The patient's muscle spasms worsened overnight, and he was found to have rhabdomyolysis with a creatinine kinase over 26,000. By midnight, he was running a fever of 102.8°F. A diagnosis of neuroleptic malignant syndrome was entertained. Amantadine and bromocriptine were administered, and the patient was given diazepam for his myoclonus. Aggressive fluid resuscitation was initiated with normal saline.

Over the next day, the patient developed respiratory distress requiring intubation and mechanical support. The patient became oligouric, and creatinine had increased from 1.04 mg/dL to 6.63 mg/dL. The decision was made to start renal replacement therapy, and the patient was transferred to a tertiary referral hospital for continuous veno-veno hemodialysis. Upon arrival, patient had increasing oxygen requirements. Rhabdomyolysis was continuing in spite of not receiving any further neuroleptics; a wider range of causes for rhabdomyolisis was obtained including tetanus and stiff person syndrome. Tetanus and rabies studies were ordered. Negative titers for glutamic acid decarboxylase made stiff person syndrome less likely. Aggressive supportive measures were continued for next 7 days.

Ultimately, punch biopsy of the neck returned a confirming diagnosis of rabies. The prognosis was discussed with the patient's family, and the decision was made to pursue a palliative course. The patient died several hours later.

Further testing identified the strain of rabies as being carried by *Lasionycteris noctivagans,* the silver-haired bat. Discussion with the family about this likely source elicited a history of bats living on the patient's property.[1]

DISCUSSION

The differential diagnosis for a patient with acute hyperthermia, muscle rigidity, and rhabdomyolosis is constituted by a number of unusual entities, such as strychnine poisioning, neuroleptic malignant syndrome (NMS), malignant hyperthermia, *Clostridium tetani* or, as in this case, rabies.[2] This patient's case would be atypical for NMS or any of the drug- or toxin-induced syndromes, since his decline continued unabated in spite of not receiving any toxic agents once hospitalized. This progressive decline was the feature that prompted the evaluation for rabies in this patient.

Despite aggressive animal vaccination and prophylaxis campaigns, rabies still claims nearly 55,000 lives annually worldwide. In the United States, 31 cases were identified between 2000 and 2009, with 45% being diagnosed postmortem.[3] Mortality for clinically apparent disease approaches 100%, with a half-dozen survivors,[4] only one of whom had not received post-exposure prophylaxis.[5]

Rabies is caused by the *Rhabdoviridae Lyssavirus*, and transmitted primarily through infected saliva in animal bites. Rare cases transmitted through tissue transplantation have been reported, and laboratory research has demonstrated the theo-

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retical possibility of aerosol transmission, but these modes remain of little clinical significance.[3]

The infection has a variable incubation period followed by a prodrome of nonspecific symptoms including fever, headache, and malaise. This progresses to the acute neurologic phase where the patient may present as encephalitic and irritable (80% of cases) or paralyzed (20% of cases). Progression into coma occurs within days of onset of the acute neurologic phase. Death is invariably heralded by multiple organ dysfunction and eventual circulatory collapse.[4]

Diagnosis of rabies is by serum, saliva, cerebrospinal fluid, and nuchal skin biopsy samples. Despite the lack of convincing human-to-human transmission, the exceptionally high fatality rate of the disease merits biosafety level (BSL) 2 precautions, and BSL-3 in select areas such as laboratories and autopsy, where concentrations of the virus may be higher.[6]

Treatment in patients who have progressed into the acute neurologic phase remains contentious, with mixed results from application of the Milwaukee protocol.[4] In the single reported survived case, a combination of antivirals and sedative medications were used to induce coma; with aggressive supportive care, the patient cleared the virus and survived, albeit with neurologic impairment.[5]

CONCLUSION

Rabies is a rare, largely preventable cause of progressive encephalopathy in the United States. Despite the reported survival of a single case of confirmed rabies, this case is more typical, with rapid decline and death from multiple organ dysfunction.

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Influenza Vaccination as a Condition of Employment for a Large Regional Health Care System

David R. Smith, MD, MPH; Bruce Van Cleave, MD

ABSTRACT

Aurora Health Care (Aurora) is a large integrated delivery system in eastern Wisconsin/northern Illinois that serves over 1.2 million patients per year and has over 30,000 employees. Aurora adopted a policy of annual influenza vaccination as a condition of employment for all employees during May 2011, to commence with the 2011-2012 influenza season. The percentage of employees vaccinated against influenza had been below 100%—the rate recommended by the Centers for Disease Control and Prevention. The intervention increased the percentage of employees vaccinated to 97.7% in the first year of implementation, compared to 71% in 2010 ($P < 0.00001$). No medical or economic reactions to this intervention were determined to be unmanageable. Aurora recommends that health systems that currently fail to achieve 90% employee influenza vaccination rates adopt a similar process.

BACKGROUND

Influenza vaccination of health care workers (HCWs) has been shown to protect patients against influenza virus infection and decrease influenza-related morbidity and mortality.[1]

HCWs are vulnerable to influenza virus infection and often serve as potential sources of influenza virus for their patients.[2] Many instances of in-hospital influenza outbreaks have been associated with unvaccinated HCWs,[3] and HCWs frequently continue to work despite being ill.[4]

HCWs represent a vital resource in times of increased demand for health care services. The Centers for Disease Control and Prevention (CDC) has recommended influenza vaccination for all HCWs since 1981.[5] The largest barrier to vaccination repeatedly has been shown to be HCWs' perceived misinformation and purported inconvenience.[5]

Since 1996, Aurora has conducted an annual HCW influenza vaccination program that involves a complex year-round partnership between the system's divisions of care management, employee health, pharmacy and logistics, information services, and communications. The multifaceted program includes decentralized distribution of vaccine, free vaccine administration, vaccination advocates, visible administrative support, and educational programs. In 2005, the system adopted a program of vaccination or active declination designed to counter misinformation related to vaccination. This was associated with a modest increase in vaccination coverage among HCWs from 2005 to 2010 (Figure 1).

In response to the early phase of the 2009 H1N1 influenza pandemic, the Infectious Diseases Society of America issued a statement supporting both seasonal and H1N1 vaccine mandates by health care institutions to protect patients against transmission of the influenza virus.[6] In November 2009, the National Patient Safety Foundation also issued a position statement supporting mandatory influenza vaccination for HCWs as a means to protect patients, fellow HCWs, and the community.[7]

Multiple health care systems throughout the United States have adopted mandatory influenza vaccination programs as a condition of employment. BJC Healthcare, a large Midwestern health care organization similar in size and revenue to Aurora, instituted a mandatory influenza vaccination program after failing to achieve an 80% vaccination rate. In the program's first year (2008-2009), the organization reported a HCW influenza vaccination rate of 98.4%.[8] Surveys of HCWs have shown that the majority of HCWs support a compulsory vaccination program.[9,10]

During the 2009 H1N1 influenza pandemic, Aurora engaged in unprecedented community and internal publicity, education, and other efforts to improve HCW influenza vaccination rates; however, the seasonal vaccination rate was not significantly different from rates the prior 2 years. The H1N1

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influenza virus was the circulating strain of influenza virus in 2009; HCWs were identified as a high priority population to vaccinate; and the monovalent H1N1 vaccine was available widely by the end of that year. Still, only 41% of the system's HCWs received the vaccine. In August 2009, senior leadership reviewed the system's influenza vaccination program and the unique challenges related to the 2009 influenza pandemic. Since 2007, the existing program was performing better than the programs of many health care systems reported in the literature prior to 2006, and similar to other systems with the same processes in place. They determined it was unlikely that HCW vaccination rates would increase significantly beyond the mid-70% range without a fundamental change. Despite the publicity during the 2009 influenza pandemic, HCWs did not adhere to internal or external calls for vaccination, putting the health care workforce—and patients—at risk. Therefore, Aurora adopted the "condition of employment" strategy in 2011 as a proven and acceptable intervention to reach nearly universal influenza protection of patients and HCWs.

METHODS

The proposal for an employment-related policy was shared with senior leadership in early 2011 and subsequently approved by the board of directors. The policy required annual influenza vaccination or an approved exemption for all employed persons both with and without direct patient contact, contracted providers, students, and volunteers ("employees") by December 31 each year. Exemptions were allowed for specific medical and religious reasons. An exemption review committee was created with members representing medicine, care management, employee health, human resources, organizational development, and legal. Medical exemptions required physician documentation of contraindications to current CDC influenza vaccination recommendations. Religious exemptions required evidence of a religious or ethical conviction that met the requirements of Title VII of the Civil Rights Act of 1964. Broad communications began immediately thereafter and continued periodically throughout the fall influenza vaccination season, emphasizing the requirement as a patient safety intervention.

Influenza vaccinations began in September 2011 and were recorded daily in the employee health database. Medical and religious exemption requests were accepted beginning August 16, and the review team met biweekly through the remainder of the vaccination season. Employee applicants or certifying physicians were contacted if further information was required to make an exemption determination. Review team determinations were shared with applicants beginning in November and recorded in the employee health database.

Managers were responsible for monitoring the vaccination/exemption status of employees in their department. Employees who were deficient in either vaccination documentation or exemption approval were notified in early December. Employees who did not have documentation of influenza vaccination or approved exemption were not scheduled to work after January 1, 2012.

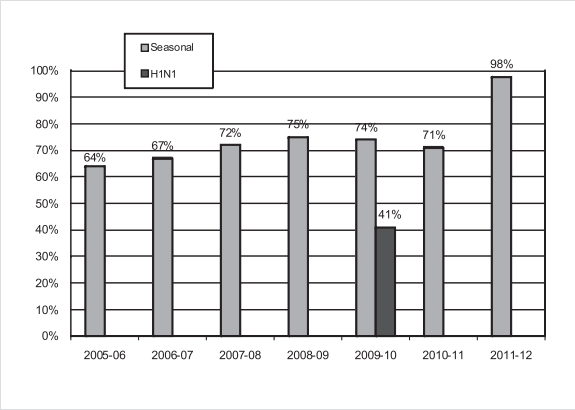

Figure 1. Percentage of employees receiving influenza vaccination during the 2005-6 through 2011-12 seasons Aurora Health Care

Table 1. 2011 Influenza Vaccination Results

	No. of HCWs	% of HCWs
Received vaccine	29,355	97.7%
Medical exemption	460	1.5%
Religious exemption	39	0.13%
Leave of absence	153	0.51%
Termination	41	0.14%
Total	**30,048**	**100%**

Abbreviations: HCW, health care workers

RESULTS

In the first year of the "condition of employment" policy, 29,355 (97.7%) of 30,048 employees received influenza vaccine (Table 1). This was significantly greater than the 71% vaccination rate of the 2010 season (χ^2 $P < 0.00001$) (Figure 1). Influenza vaccinations began the first week of October. The increase in vaccination rate was apparent by week 2 of the vaccination period (Figure 2).

There were a total of 637 exemption requests: 546 medical requests and 91 religious requests. Of these, 460 (1.5%) medical waivers and 39 (0.13%) religious waivers were accepted (Table 2). Additionally, 153 HCWs on a leave of absence or disability during the vaccination period were expected to show evidence of influenza vaccination prior to returning to work.

The voluntary resignation of 2 full-time and 9 part-time

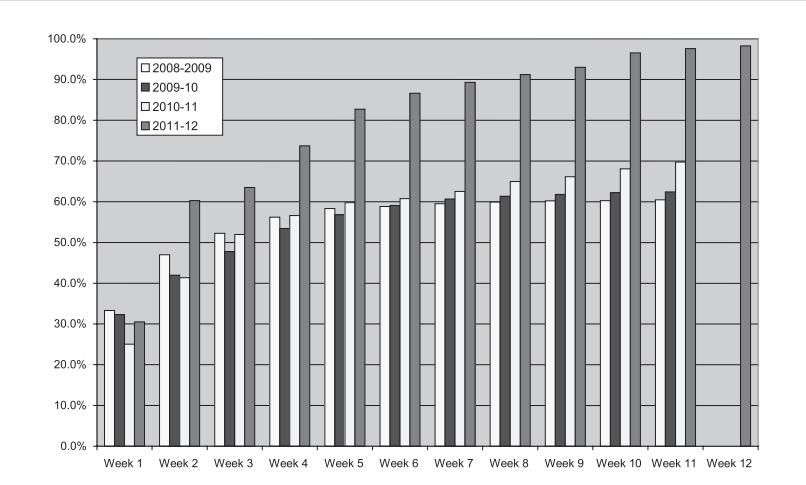

Figure 2, Percentage of employees receiving influenza vaccination by week during the vaccination period 2008-09 through 2011-12 seasons at Aurora Health Care.
Week 1=first week of October

Table 2. 2011 Influenza Vaccination Exemption Rates

	Exemptions	
	Approved	**Rejected**
Total (N= 637)	**499 (78%)**	**138 (22%)**
Medical (n=546)	460 (84%)	86 (16%)
Egg allergy	129	
Vaccine reaction	211	
Gullian Barre Syndrome / neurologic	70	
Other	50	
Religious (n= 91)	39 (43%)	52 (57%)

HCWs was attributed to the vaccination requirement. In addition to full- and part-time employment categories, the system uses the category "zero assigned hours," which refers to HCWs who may be requested to work in times of increased patient volume. The resignation of 30 "zero assigned" HCWs was attributed to the requirement.

DISCUSSION

The adoption of an influenza vaccination policy as a condition of employment was a successful patient safety intervention for the system. The processes employed, and the results achieved are similar to those reported by BJC Healthcare.[9]

Secondary objectives included the implementation of medical exemption processes to maximize HCW safety and religious exemption processes to support the organization's value of respecting diversity. The religious exemption process required the HCW to submit a statement describing how influenza vaccination would violate one's deep-seated belief system, and participate in a telephone interview if the exemption review team felt more information was necessary to make a determination. Legal counsel assisted the review team in developing standardized interview questions and criteria, which provided a consistent defensible framework.

Another secondary objective was to minimize any disruption of patient service through HCW dissatisfaction or influenza-related illness.

Many important questions related to these secondary objectives could not be measured due to limitations in the existing data systems. Adverse events related to vaccination and workers compensation are tracked in a single employee health database. There were 15 influenza vaccination workers compensation claims filed in 2011. The database does not allow a direct comparison to influenza vaccination-related workers compensation claims the previous year. One hospitalization occurred following vaccination of a HCW who had not been vaccinated before, and had not completed a request for an exemption. An independent medical examination opined that the vaccination was not a causal factor.

Minor adverse events were those that did not result in any lost working time or need for medical treatment. A formal analysis of the incidence of minor adverse events was not carried out. An informal assessment suggests a modest increase in the number of minor adverse events, due in part to a larger number of HCWs vaccinated and the heightened visibility of the mandatory program.

Service disruption to patients did not occur. Employed physicians and other clinicians were subject to the same requirement. The 1 union representing nursing was involved early in planning and was an effective and supportive partner. We strongly recommend that union representation participate throughout the process. Of the 11 regularly scheduled HCWs who resigned, 6 had requested exemptions. One of the 9 part-time HCWs who resigned already had submitted a resignation to take a position in early 2012 with a different employer, and one received the influenza vaccine in late December but chose to resign nonetheless. The 30 HCWs who were in the category of "zero assigned hours" were available to work only on an "as-needed" basis, and may not have worked for the organization in the recent past. Only 4 HCWs in this category requested an exemption.

Aurora has a formal process for measuring HCW job satisfaction, but the process did not include questions about the

vaccination policy. Positive and negative informal feedback was received from HCWs in the form of e-mail, letters, and flyers. The authors responded individually to those who provided feedback. The corporate communications department managed inquiries from local news media to emphasize the patient safety message, and to address concerns related to individual autonomy and vaccine related misinformation.

The organization did not have a means to measure HCW absence due to acute illness. The 2011-2012 influenza season in Wisconsin was mild.[11] Had such a measure of HCW absence existed, it is not believed that any difference would be seen.

Senior leadership support was critical to the program's success and its continuation. Policy modifications are being considered for 2012-2013. It proved challenging to evaluate late exemption requests over the holidays and meet the December 31 deadline. A November 15 date for vaccination has been proposed. The existing policy does not include 1072 nonemployed physician and advanced practitioners working in the system's facilities. Expanding the scope to include these clinicians is being explored.

Adoption of a similar process among health care systems that fail to achieve 90% employee vaccination rates has been proposed by the National Vaccine Advisory Committee. Such a program would have the greatest impact during severe influenza seasons, which disproportionally affect HCWs who must be available to serve the public.

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Proceedings from the 2011 Annual Meeting of the American College of Physicians, Wisconsin Chapter

The Wisconsin Chapter of the American College of Physicians held its annual meeting in Wisconsin Dells, September 9-11, 2011. Internal medicine residents from each of Wisconsin's 5 residency programs presented their research and/or unusual clinical experiences via posters and vignettes.

PRESENTED POSTERS

Effect of Hyperglycemia on Outcomes in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Narendranath Epperla, MD, Yusuf Kasirye, MD, Melissa Simpson, PhD, Hong Liang, PhD, Chaitanya Mamillapalli, MD, Steven Yale, MD; Departments of Internal Medicine, Biostatistics, and Clinical Research and Marshfield Clinic Research Foundation; Marshfield Clinic, Marshfield, Wis

Background: Hyperglycemia is associated with adverse health outcomes independent of its associated metabolic disease states. However, little evidence exists concerning hyperglycemia and outcomes associated with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). This study examined blood glucose (BG) during AECOPD hospitalization and clinical outcomes. We hypothesized that increased BG is associated with worse clinical outcomes.

Methods: We retrospectively studied a cohort of 215 hospitalized patients (40 to 80 years of age) with physician-validated AECOPD from January 1, 2004 to December 31, 2008. Inclusion criteria for this study were a diagnosis of AECOPD at admission and discharge, and BG obtained within 6 hours of hospital presentation. Regression analyses accounting for repeated BG measurements during hospitalization were performed to estimate the odds ratio (OR) for daily mean BG and length of hospitalization, hospital readmission, and 90-day all-cause mortality.

Results: Mean length of hospitalization was 3 days. Adjusting for age and diabetes, decreased BG was associated with longer length of hospitalization (OR, 0.72, 95% CI, 0.54-0.96, $P=0.03$). Forty-one patients (19%) were readmitted to the hospital within 30 days of discharge from index hospitalization. Adjusting for previous covariates and length of hospitalization, BG was not associated with 30-day hospital readmission (OR, 0.82, 95% CI, 0.54-1.22, $P=0.32$). Nine patients (4%) died within 90 days of their index hospitalization. Adjusting for previous covariates and readmission, decreased BG was associated with increased odds of 90-day all-cause mortality (OR, 0.30, 95% CI, 0.11-0.86, $P=0.02$).

Conclusion: Decreased BG levels were associated with a longer hospitalization and 90-day all-cause mortality, suggesting that BG during hospitalization may be indicative of overall health and therefore may be a useful prognostic tool. Blood glucose response (or lack thereof) in light of hyperglycemic agents (96% of cohort received corticosteroids during hospitalization) may be a proxy for a patient's overall physiological status.

Eosinophilic Esophagitis: An Escalating Epidemic?

Rajesh B Kethireddy, MD, Camille Torbey, MD, Jeffrey Resnick, MD; Departments of Internal Medicine-Pediatrics, Gastroenterology, and Pathology; Marshfield Clinic, Marshfield, Wis

Background: Eosinophilic Esophagitis (EE) is a relatively "new" clinicopathological entity characterized by chronic esophagitis and dense eosinophilia of the esophageal mucosa. We sought to determine the incidence of EE, observe the incidence trends between 1995-1997 and 2005-2007, and evaluate the temporal relationship between onset of atopic dermatitis (AD) and EE diagnosis.

Methods: A retrospective cohort study was conducted in a population-based cohort. Esophageal biopsy reports from 1995-1997 and 2005-2007 were screened using SNOMED (Systematized Nomenclature of Medicine) to identify patients with pathologic confirmed or suspected EE. Histopathology reports in which EE could not be excluded and those with features suggestive of EE were reviewed. Cases of esophagitis due to chemicals, drugs, infections, inflammation, and structural abnormalities (tumors, strictures, ulcers) were excluded. A single pathologist blinded to clinical, endoscopic features, and histopathology diagnosis reviewed 373 tissue specimens. Medical records of confirmed EE cases were reviewed to determine associated atopic dermatitis based on American Academy of Dermatology (AAD) criteria, clinical presentation, macroscopic findings on endoscopy, and site of biopsy.

Results: Twenty-seven cases of EE were positively confirmed: 20 adults and 7 children. Median age at diagnosis was 32.1 years. Though 9 patients had some features of AD, none met all the major criteria set by AAD. There was a significant increase in the incidence rates of EE in the study population from 1995-1997 compared to 2005-2007 (2.76 vs 13.6 cases per 100,000 person years). Similarly increased incidence rates were observed in both female (1.91 vs 11.4 cases per 100,000 person years) and male (4.37 vs 18.2 cases per 100,000 person years) populations.

Conclusions: Given the stability of demographic conditions and health care access, our study demonstrates an increase in

incidence of EE from 1995 to 2007 in a population-based cohort that cannot be attributed to misclassification or misdiagnosis. There was no significant association between atopic dermatitis and EE. These findings suggest that EE may be more common than previously realized. Identifying factors that contribute to this increased risk should be subject to further investigations.

Long-term Glycemic Control in Diabetes Mellitus Patients Started on U-500 Regular Insulin

Rachel McKenney, MD, Mary Frohnauer, MD, Jacob Gundrum, MS; Gundersen Lutheran Medical Foundation, La Crosse, Wis

Background: Glycemic control in types 1 and 2 diabetes mellitus has become more challenging with the rising obesity epidemic. In patients who require insulin doses exceeding 200 units/day, using U-100 regular insulin may not provide adequate glycemic control because of either poorly absorbed subcutaneous depositions or unreliable absorption patterns.

Methods: This study's purpose was to test the hypothesis that switching from U-100 regular insulin to U-500 regular insulin improves long-term glycemic control in diabetic patients who have not attained glycemic control. A retrospective review was conducted for these patients with U-500 begin dates between January 2005 and December 2010.

The primary measure of long-term glycemic control is a long-term reduction in hemoglobin A1C (Ha1c). This is defined at a time point greater than 8 months post U-500 initiation and ending either when the patient discontinued the use of U-500 insulin or at the latest available date. Secondary endpoints studied included change in body mass index (BMI) after initiation of U-500 insulin and change in 6-month Ha1c (collected between 4 and 8 months post U-500 initiation).

Results: The mean change in Ha1c for long-term analysis (n=68) was -1.11±1.95 with *P* value of <0.001 (95% CI: -1.58 to -0.64). The mean long-term follow-up was 35.78±22.62 months with minimum of 9.17 and maximum of 93.99. The mean change in Ha1c after approximately 6 months (n=44) was -1.32±1.66 with a *P* value of <0.001 (95% CI, -1.82 to -0.81); mean change in BMI at 6 months was 0.67±2.42 ($P = 0.082$) and 1.55±5.39 ($P = 0.021$) at the latest date.

Conclusion: U-500 may improve glycemic control, both in the short term and long term for those patients in whom glycemic control is not achieved with U-100 insulin. There does appear to be a small increase in BMI in the long term. One needs to take this into account when deciding whether or not to use U-500. However, this alone should not deter a clinician from considering the use of U-500.

Working Beyond the Duty Hour Rules

Sarah J. Nickoloff, Kathlyn E. Fletcher; Medical College of Wisconsin, Milwaukee, Wis

Background: The Accreditation Council for Graduate Medical Education (ACGME) recently announced new guidelines that will allow occasional exceptions to the duty hour rules in very limited circumstances. This study assessed the frequency and circumstances in which house staff might use these exceptions.

Methods: We conducted a cross-sectional survey study of internal medicine house staff at a single academic tertiary care hospital. The anonymous survey asked about the 2 prior weeks of ward service and whether participants would have used the anticipated exceptions, if allowed. Participants also were asked to provide brief descriptions of situations.

Results: Fifty-nine percent of the surveys were returned. Interns and residents each accounted for 50% of the total. Sixty-nine percent indicated they had wanted to stay longer than current duty hour rules allowed. Of those, 55% would have broken the 24+6 hour rule; 33%, the 10-hour rule; and 12%, the 80-hour rule. Continuity for an unstable patient was the most common reason cited for wanting to stay. Humanistic attention for the family or patient and educational opportunities also were cited frequently. Descriptions of these situations illustrated several themes, including concerns for workload, patient acuity, critical decision points in patient care, and doctor-patient communication.

Conclusions: Nearly 70% of house staff identified at least 1 time in the preceding 2 weeks that they wanted to exceed current duty hours. The majority involved providing continuity for an acutely ill patient; however, the doctor-patient relationship, humanistic attention to patients, and workload also were commonly cited. We conclude that after July 1, situations will routinely arise during which house staff will want to stay beyond duty hours, and this may occur more frequently than anticipated by the ACGME.

Resident-Driven Quality Improvement

Pinky Patel, Karrie Martin, Zouyan Lu; Medical College of Wisconsin, Milwaukee, Wis

Background: There are more than 51,000 deaths in the United States each year from colorectal cancer (CRC) and more than 500,000 patients receiving treatment for end-stage renal disease. Early diagnosis and prevention of both CRC and chronic kidney disease (CKD) leads to better outcomes for patients, making these optimal areas of concentration for quality improvement (QI) initiatives. Using the Wisconsin Collaborative for Healthcare Quality (WCHQ) as a guide for the development and measurement of residents' QI interventions, the Internal Medicine residency program at the Medical College of Wisconsin (MCW) formulated academic, year-long projects to improve outcomes in both CRC screening and health markers in CKD.

Methods: For the CRC project, chart review of clinic patients identified those appropriate for a targeted QI intervention. Different clinic sites implemented strategies for their specific populations and residents' interventions, including reminder letters and patient information pamphlets on the importance of CRC screening. Chart review also was performed to identify patients with at least Stage III CKD. Interventions included frequent follow-up for blood pressure (BP) monitoring, increased low-density lipoprotein (LDL) control, and increased testing for proteinuria. Changes to the electronic medical

record also were introduced to facilitate appropriate interventions for patients with CKD. Outcomes for CRC screening and BP/LDL goals in CKD patients were measured before and after the interventions.

Results: Initial data from the 2009-2010 academic year QI project showed that residents' comfort using QI measurement to improve their clinical skill increased from 52% to 85% after the educational intervention. For the CRC project, evaluation by remaining residents 1 year post-intervention showed increased CRC screening rates across all clinic sites. This includes colonoscopies and other CRC screening modalities. Less data is available for the ongoing CKD project. Mid-intervention review reveals that blood pressure and cholesterol control have improved.

Discussion: Overall, residents have responded positively to the program and have been enthusiastic about implementing the interventions. For both QI projects, resident education on quality improvement as well as on the specific clinical disease being targeted was integral to the program's success. The CRC QI project clearly improved screening rates. Initially, it appears that residents are identifying and treating chronic kidney disease more appropriately.

Omega-3 Polyunsaturated Fatty Acids Decrease Caveolin Expression in Cardiac Fibroblasts: One Possible Mechanism of Fish Oil's Cardiac Benefits

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Background: Heart failure is the leading reason for hospital admissions and is the most costly Medicare expenditure. About half of heart failure cases are due to diastolic dysfunction. One of the main causes of diastolic dysfunction is cardiac fibrosis. Previous study demonstrated that Omega-3 polyunsaturated fatty acids (ω-3 PUFAs, eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA]) prevent overload-induced cardiac fibrosis and cardiac dysfunction by blocking transforming growth factor β1-induced phospho-Smad2/3 nuclear translocation through activation of the cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathway in cardiac fibroblasts. Previous study also demonstrated that in cardiac fibroblast, EPA and DHA increase cGMP levels by increasing phospho-eNOS and eNOS protein levels and nitric oxide production. Caveolin is the principal structural protein in caveolae, which interacts with endothelial NOS (eNOS) and leads to eNOS inhibition. Therefore, we tested the hypothesis that EPA and DHA decrease caveolin expression in cardiac fibroblasts.

Methods/Results: Confluent cultures of adult mouse cardiac fibroblasts in 6-cm collagen-coated plates were incubated in the presence or absence of the indicated control, DHA or EPA for 24 hours. Western Blot analysis was carried out to determine protein levels of caveolin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). GAPDH was used as the internal control. Compared with control, DHA (10 mM) and EPA (10 mM) significantly reduced caveolin/GAPDH ratio in cardiac fibroblasts (72% and 65% reduction, respectively $P < 0.05$)

Conclusions: DHA and EPA decrease caveolin expression in cardiac fibroblasts. This study suggests that EPA and DHA increase intracellular levels of eNOS by decreasing caveolin expression in cardiac fibroblasts. Future study is warranted to examine whether over-expression of caveolin in cardiac fibroblast attenuate the EPA- and DHA-induced eNOS activation.

DISPLAYED POSTERS

Testicular Mesothelioma?

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Introduction: Malignant mesothelioma of the tunica vaginalis testis is an aggressive and rare neoplasm, representing less than 5% of all malignant mesothelioma. There are fewer than 200 cases reported to date. It presents as a hydrocele or an intrascrotal mass, and most diagnoses are made from post-operative histopathology. Previous asbestos exposure is reported in 30% to 40% of reported cases.

Case: A 40-year-old African-American man with a past medical history of hypertension and hyperlipidemia presented with left testicular swelling and dull aching pain of 4 months. He had generalized fatigue and unintentional weight loss of 20 pounds in the last 4 months. He denied any trauma to his scrotal area, history of asbestos exposure, or family history of cancer.

On physical examination, he appeared well with stable vital signs. There was no palpable lymphadenopathy. Lung and cardiac examinations were unremarkable. There was no gynecomastia. The abdomen was nontender, and the liver and spleen were not palpable. Left hemiscrotum was markedly enlarged and firm, nontender, and without discrete mass. The right scrotum was normal in size without tenderness or indurations, and he exhibited no extremity edema. Hemogram, liver, and renal function tests and testicular tumor markers were normal. Computed tomography (CT) study showed partially visualized left testicular mass and hydrocele without retroperitoneal, intra-abdominal pelvic laparoscopy. The remainder of the chest, abdomen, and pelvis were normal. Following a diagnosis of left hydrocele, hydrocelectomy showed a nodular swelling along the testis. Histopathology and immunohistochemical report from the paratesticular mass and hydrocele sac was signed out as papillary mesothelia lesion that showed microscopic early invasion. After the histopathology, definitive treatment with left orchiectomy and hemiscrotectomy was done. The patient subsequently was treated with adjuvant chemotherapy with 2 cycles of Alimta and cisplatin. Due to his deteriorating creatinine clearance, cisplatin was switched to carboplatin. Twenty months after diagnosis, the patient was free of metastasis.

Conclusion: Our patient had an unusual neoplasm, mesothelioma of tunica vaginalis testis primarily involving the testes. Because of this clinical scenario's rarity, treatment recommendations are not standardized.

Applying the principles derived from experience with the treatment of mesothelioma of the lung and from limited experience with the management of testicular mesothelioma, we can devise an adjuvant chemotherapy regimen and follow-up modality that may offer good long-term survival. We also recommend post-hydrocelectomy histopathological analysis.

Neutrophilic Eccrine Hidradentis in a Patient with Myelodysplastic Syndrome Receiving G-CSF

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Introduction: Skin rashes are a common and frequently nonspecific finding with varying clinical significance. They are often a manifestation of an underlying process such as infection, autoimmunity, malignancy, or medication reaction. For many clinicians, these findings pose a diagnostic challenge and it may be difficult to determine the exact etiology.

Case: A 54-year-old man with a history of myelodysplastic syndrome was admitted for fever. On admission, his white blood cell (WBC) count was 1.25 K/uL with an absolute neutrophil count (ANC) of 0.490 K/uL. In addition to fever, he complained of right upper quadrant pain. Imaging was negative for acute abdominal pathology. However, he was started on ertapenem for a suspected intra-abdominal infection. Over the course of 3 days his abdominal pain improved but his low-grade fever persisted. On day 4, he spiked a fever of 40°C, and his ANC dropped to 0.08. As a result, he was given granulocyte colony stimulating tactor (G-CSF). Due to continued fever and dropping ANC, on hospital day 6, he was given another dose of G-CSF. That same day, he was found to have developed a nonpruritic, erythematous, maculopapular rash that involved primarily his chest, abdomen, legs, and arms. Skin biopsies were obtained and results were consistent with a diagnosis of neutrophilic eccrine hidradenitis (NEH).

Discussion: NEH is an extremely rare inflammatory skin reaction commonly seen in patients undergoing chemotherapy for hematologic malignancies. It also has been reported in healthy patients, patients with solid malignancies, infections, and in association with certain medications. The eruptions are often seen in neutropenic patients presenting with fever. It is characterized by the sudden onset of erythematous papules and plaques that can affect the trunk, arms, legs, and face including the periorbital region. Lesions are typically asymptomatic but can be tender and pruritic. A biopsy is required for diagnosis, and histology classically reveals neutrophilic infiltration of the eccrine glands with accompanying necrosis. The pathophysiology is not understood entirely but thought to be due to the direct toxic effect of the offending agent in the sweat glands. Another theory is that NEH is part of the spectrum of neutrophilic dermatoses. NEH is self-limiting and resolves spontaneously within 1 to 2 weeks without any long-term sequelae. Steroids, nonsteriodal anti-inflammatory drugs (NSAIDs), and antibiotics have been used for symptom control and to decrease duration. Dapsone also has been suggested for prevention of recurrent NEH.

Not Just Another Viral Syndrome

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Introduction: Acute disseminated encephalomyelitis (ADEM) is a disorder characterized by a monophasic inflammatory demyelination of the central nervous system (CNS). Most cases have been identified in children and usually follow one of the exanthematous diseases, but it also may present with similar clinical features in adult patients.

Case: A 23-year-old woman with no significant past medical problems presented with persistent fever and neck/back pain. She had been evaluated at an outside hospital 2 weeks prior to the current presentation and was treated for aseptic meningitis based on inconclusive imaging and cerebrospinal fluid (CSF) analysis. Pertinent physical exam findings were pain with cervical flexion, bilateral lower extremity weakness, and central visual field defect of the left eye. Her laboratory evaluation revealed leukocytosis, antinuclear antibody negative, rheumatoid factor positive, and elevated serum antistreptolysin-O titer and C-reactive protein. Brain magnetic resonance imaging (MRI) showed new areas of supratentorial white matter signal intensities and bilateral optic nerve enhancement. CSF findings were significant for high opening pressure, lymphocytic pleocytosis, low glucose/high protein, but negative oligoclonal bands. As the hospital course progressed, the only other significant laboratory findings were the positive IgG and IgM *Mycoplasma* serologies. Given the patient's improvement with steroids, MRI findings, and the otherwise negative infectious workup, she was given the working diagnosis of ADEM. A course of systemic corticosteroids, azithromycin, and ciprofloxacin were completed, and the patient made a full recovery.

Discussion: ADEM typically presents with an acute onset of focal neurological signs within days to weeks of an initial nonspecific viral illness or vaccination. It usually follows a monophasic course, and this allows ADEM to be differentiated from multiple sclerosis (MS). However, recently reported adult cases have demonstrated multiphasic presentations; consequently there has been increased reliance on MRI for diagnosis. The radiographic patterns generally are multifocal asymmetric lesions that mainly involve the supratentorial white matter. Key differentiating factors between ADEM and MS are atypical clinical symptoms of MS, absence of oligoclonal bands in CSF, and eventual gray matter involvement. Successful management strategies include corticosteroids, plasma exchange, and intravenous immunoglobulin. Outcome of ADEM is generally favorable in the pediatric population but mortality levels in adults can be high, especially in patients requiring intensive care unit admission or presenting with multiphasic forms.

A Rare Complication Associated with Graves' Disease

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Introduction: Graves' disease is an autoimmune disease that results in an overactive thyroid gland. Autoantibodies act to stimulate the thyroid stimulating hormone (TSH) receptor ultimately leading to an excessive production of T_3 and T_4. Several autoimmune diseases like Graves' disease are known rarely to be associated with neutropenia.

Case: A 33-year-old African-American woman presented with a 1-year history of palpitations, poor appetite, weight loss, lightheadedness, and heat intolerance that had worsened acutely 2 weeks prior to admission. She had a history of Graves' hyperthyroidism that was diagnosed 2 years prior. At the time of diagnosis, she was started on methimazole, but she discontinued the medication about 6 months prior to admission because she felt it was no longer controlling her symptoms. On physical exam, her pulse was 130. She appeared flushed and mildly diaphoretic. She had mild exophthalmos but no lid lag. Her thyroid gland was tender to palpation and markedly enlarged. Her reflexes were hyperactive. On admission, her TSH was undetectable, free T_3 >32.6 pg/ml, and free T_4 >7.77 ng/ml. She also was found to be leukopenic with a white blood cell count of 2600/cu ml and an absolute neutrophil count of 670/cu ml. The patient was admitted with severe thyrotoxicosis secondary to Graves' disease. Her leukopenia and neutropenia were thought to be due to an autoimmune process rather than methimazole. She was started on propylthiouracil and prednisone for her hyperthyroidism and propranolol for symptom control. She was referred to endocrine surgery for definitive management of her Graves' disease.

Discussion: The association between Graves' disease and neutropenia is thought to be due to the production of antineutrophil autoantibodies. It also is speculated that the autoantibodies against the TSH receptor may cross react with thyrotropin binding moieties on neutrophils leading to neutrophil destruction. The treatment for neutropenia secondary to Graves' disease is regulating thyroid function. In addition, methimazole rarely causes agranulocytosis resulting in neutropenia; but in the case described above, this was very unlikely as the patient had been off methimazole for months. It is important to recognize this rare complication associated with Graves' disease and to promptly treat the underlying thyroid dysfunction.

Relationship Between Body Composition and Glomerular Filtration Rate Estimates in the General Population

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Background: Differences in body composition, (ie, lean mass or lean mass percentage) may be responsible for imprecision in estimated glomerular filtration rate (eGFR) estimates from serum creatinine. In this study, we examined the relationship between the eGFR and anthropometric and body composition measures in a large cohort.

Methods: We analyzed data from a cross-sectional study on bone health comprising 1630 randomly selected community-dwelling adults 30 to 86 years old. The Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were used to calculate eGFR from IMDS-standardized serum creatinine. Body mass index (BMI) and body surface area (BSA) were calculated from measured height and weight. Body composition was determined by dual-energy x-ray absorptiometry, and grip strength was measured. Linear regression models adjusted for age, hypertension, diabetes, and smoking were used to examine the association between eGFR and the variables of interest.

Results: In the fully adjusted models in women, eGFR-MDRD was inversely associated with height ($\beta = -0.08$; $p = 0.012$), lean mass percentage ($\beta = -0.06$; $p = 0.047$), and grip strength ($\beta = -0.15$; $p < 0.001$), and eGFR-CKD-EPI was inversely associated with grip strength ($\beta = -0.08$; $p = 0.001$). In men, there was an inverse association between eGFR-MDRD and lean mass percentage ($\beta = -0.10$; $p = 0.013$) and grip strength ($\beta = -0.12$; $p = 0.022$) and between eGFR-CKD-EPI and lean mass percentage ($\beta = -0.07$; $p = 0.018$). However, there was no association between eGFR calculated using either of the 2 equations and weight, BMI, BSA, lean mass, or fat mass.

Conclusions: The inverse relationship between eGFR and measures of muscle mass and muscle strength suggest that incorporation of these variables might improve eGFR prediction from serum creatinine in the general population.

Spontaneous Hemorrhage into the Mediastinum from a Parathyroid Adenoma

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Introduction: Extracapsular hemorrhage of a parathyroid adenoma is extremely rare yet should be considered in a patient presenting with spontaneous bleeding in the neck and mediastinum. The etiology of this occurrence is currently unknown. Elevated PTH (parathyroid hormone) and calcium levels with specific radiological findings are useful in diagnosis.

Case: A previously healthy 56-year-old female presented with a 3-day history of progressive intermittent left neck pain and dysphagia. She denied fever, chills, weight loss, recent trauma, history of hyperparathyroidism, anticoagulation, or NSAID use. On physical examination, the patient was afebrile with fullness over the left lower neck without ecchymosis. CT of the chest and neck was suggestive of an inflammatory process involving the superior and

posterior mediastinum and an ill-defined, enhancing mass in the left tracheoesophageal groove, starting at the midportion of the posterior aspect of the thyroid.

Laboratory studies showed WBC 4.9 x 10^3/uL, hemoglobin 12 g/dl, serum calcium 11.1 mg/dl (normal 8.5-10.3 mg/dl), and ionized calcium 6.5 mg/dl (normal 4.7-5.5 mg/dl). PTH was elevated at 101 pg/ml (normal 7-53 pg/ml). Her hemoglobin dropped to 8.9 g/dl over the next 3 days although she remained hemodynamically stable. MRI of the chest and neck showed a diffuse process within the lower neck extending into the superior mediastinum suggestive of a hematoma with bilateral pleural effusions. Left neck exploration showed an enlarged left superior parathyroid adenoma with surrounding blood clot and fibrin. Symptoms resolved postoperatively with normalization of PTH and serum calcium levels. A subsequent chest x-ray revealed complete resolution of the pleural effusions.

Discussion: Spontaneous hemorrhage of a parathyroid adenoma is extremely rare. Hemorrhage may be confined to the capsule or extend, as in this case, extracapsularly. Symptoms depend on the size of the adenoma and hematoma and may include a neck mass, swelling, pain or discomfort, bruising, ecchymoses, dysphagia, hoarseness, or dyspnea. Predisposing factors include trauma, use of anticoagulants or NSAIDs, and the imbalance between the growth of the adenoma and available vascular supply. Diagnosis of spontaneous rupture of a parathyroid adenoma without provoking factors is challenging. A high index of clinical suspicion is required in order to make an accurate diagnosis.

Propylthiouracil: Suppressing More Than Thyroid Hormone

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Case: A 56-year-old woman with a past medical history of Graves' disease presented with a chief complaint of fever, chills, nonproductive cough, and general malaise for 4 weeks. Her symptoms began immediately after initiation of propylthiouracil (PTU) therapy for recurrence of hyperthyroidism, though she failed to report this until the day before admission. She was diagnosed with Graves' disease in 1996 and initially treated with methimazole. However, she did not tolerate this and was switched to PTU. She received this therapy for 2 years, after which time it was stopped due to remission of her disease. At this presentation, the patient had a temperature of 100.3°F, rigors, exudative tonsil lesions, and an erythematous pharynx. She had a mild normocytic anemia (hemoglobin 9.2 g/dL) and thrombocytopenia (platelet count 123 e3/uL), but more substantially her white blood cell count (WBC) was 1.3x10^9/L with an absolute neutrophil count of zero, TSH was 0.015 µU/mL. PTU was discontinued after consultation with hematology affirmed concern for PTU-induced pancytopenia. She was not started on granulocyte colony stimulating factors (GCSF) since little evidence suggested a benefit in PTU-induced agranulocytosis. The patient had recovery of neutrophils on hospital day 10 to 1.8x10^9/L. Her neutrophils remained above 1.5 x10^9/L during the remainder of the hospital stay, and she had a WBC of 4.8 x10^9/L, hemoglobin 11.8g/dL, and platelet count of 265e3/uL on the day of discharge. She underwent radioactive iodine ablation (RAI) for definitive treatment.

Discussion: Thionamides (PTU and methimazole) are first-line options for treatment of Graves' disease, with methimazole being preferred in nonpregnant patients since it is more effective with fewer side effects. Agranulocytosis is a rare, serious complication of thionamides occurring in 0.3% of patients, with pancytopenia being even more rare. Therefore, physicians and patients must be aware of symptoms of agranulocytosis, discontinue the medication, and perform further evaluation immediately. Routine monitoring is not recommended since agranulocytosis develops suddenly, though typically within the first 3 months of therapy. The median time to resolution of agranulocytosis is 10 to 14 days. Case reports and a small prospective study have not shown an improvement in recovery times with G-CSF. Instead, discontinuation of the thionamide and supportive treatment with antibiotics for neutropenic fever is recommended. Then either RAI or thyroidectomy should be pursued for definitive treatment.

Another Great Masquerader

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Introduction: Human immunodeficiency virus (HIV) is an increasingly prevalent disease, and early diagnosis is important to prevent the spread of infection and to begin prompt treatment. Acute retroviral syndrome (ARS) describes the clinical signs and symptoms of primary HIV infection, which includes the period from initial HIV infection to HIV seroconversion.

Case: A 19-year-old man with a past medical history of chronic constipation and seasonal allergies presented with complaints of rectal pain for 1 week along with fever, chills, and malaise. Prior to presentation, he had been evaluated at an outside hospital and underwent a rectal exam under anesthesia with no identification of abnormalities. On presentation at our institution, physical exam was significant for a low-grade fever, maculopapular rash on his torso, and perianal mucosal ulcerations. Initial lab evaluation was significant for elevation of hepatic transaminases and thrombocytopenia. He was admitted for further treatment and evaluation, and ceftriaxone was initiated to cover for Gram-positive bacterial infections, including sexually transmitted diseases. Rectal swabs were negative for herpes simplex virus (HSV) and bacteria, including group A streptococcus and *H. ducyeri.* Further laboratory workup was negative for viral hepatitis, syphilis, gonorrhea, and chlamydia. Initial HIV antibody assay also was negative, but serum HSV serologies (IgG and IgM) were positive. When informed of his HSV infection, the patient admitted to having 13

male sexual partners in the last year, which prompted concern for an acute retroviral infection. HIV RNA polymerase chain reaction (PCR) was ordered and revealed an HIV viral load of over 700,000. The patient was discharged home with outpatient infectious disease clinic follow-up. As an outpatient, antiretroviral medications were started, and the patient's HIV viral load eventually became undetectable after 6 months of therapy.

Discussion: The initial presenting signs and symptoms of acute retroviral syndrome are often nonspecific. The most common presentation is an acute mononucleosis-like illness characterized by fever, sore throat, and lymphadenopathy. Other symptoms include lethargy, malaise, myalgias, weight loss, headache, and a diffuse maculopapular rash. Acute retroviral syndrome also can involve multiple organ systems. Muscosal ulcerations of the oropharynx, esophagus, and the genitalia have been reported to occur in 28%, 17%, and 6% of patients respectively. Involvement of the gastrointestinal system can include vomiting and diarrhea along with pancreatitis, colitis, and epiglottitis. Hepatitis is a common presentation that often resolves as the host's immune system gains control over the initial viral replication. Other laboratory abnormalities include anemia, leucopenia, and thrombocytopenia. Neurologic involvement most commonly includes headaches but also can include aseptic meningitis or encephalitis. The signs and symptoms of ARS usually begin within 2 to 4 weeks of initial HIV infection and last approximately 2 to 3 weeks. During the primary HIV infection, the viral load is very high and the patient is highly infectious. Early identification is important, not only for initiation of antiretroviral therapy to preserve the host's immune responses, but also to decrease transmission through patient education and therapy. Clinicians should have a high index of suspicion of ARS in patients with generalized mononucleosis-like symptoms and risk factors for HIV infection.

Fulminant Pseudomembranous Colitis

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Introduction: Clostridium difficile is a cause of pseudomembranous colitis that commonly presents as diarrhea after antibiotic use. Diagnosis of this disease may be difficult in patients with other chronic gastrointestinal disease and may lead to increased morbidity and mortality.

Case: A 45-year-old woman with celiac disease presented with diarrhea, vomiting, abdominal pain, laryngitis, rhinitis, and fever. She had not been adhering strictly to a gluten-free diet, and she recently had undergone treatment with cephalexin for a toenail infection. She also was exposed to sick contacts through her employment at an assisted living facility. Initially, she was started on zanamivir for likely influenza infection, and she returned home. The next day her symptoms became worse and she reported to a different clinic where she was referred to the emergency department (ED) due to dehydration and an acutely tender abdomen. On examination, her abdomen was soft but tender in the periumbilical region with guarding. Abdominal CT revealed pancolitis but no free air. Her white blood cell count was 18,100/mm3, and her stool *C. difficile* nucleic acid amplification test (NAAT) was positive. She felt significantly better the next day after receiving intravenous (IV) hydration, oral vancomycin, and antiemetics. She was discharged home on metronidazole and recovered to her baseline over the next 3 days. She then had a recurrence of symptoms 11 days later and reported to the ED. She again tested positive for *C. difficile* and was started on oral vancomycin and IV metronidazole. Her abdomen was soft but more tender than before. On hospital day 2 her abdominal pain and diarrhea worsened significantly. Surgery was consulted and an exploratory laparotomy was deemed necessary. She underwent total colectomy with end colostomy. Her condition improved after surgery, and the rest of her hospital stay was uneventful.

Discussion: C. difficile is a spore-forming Gram-positive rod that produces 2 exotoxins (A and B) and typically causes infections in the setting of antibiotic use and immunosuppression. It is believed that alterations in the normal flora caused by antibiotics and immune dysfunction allow *C. difficile* competitive and selective advantage in the gut flora. Exposure to the bacteria at the time of antibiotic use is not always necessary due to its presence in the normal flora of 2% to 5% of the general population. The clinical presentation can range from a few days of mild diarrhea to life-threatening pseudomembranous colitis. Although *C. difficile* is a well-known cause of diarrhea, diagnosis in patients with other gastrointestinal diseases sometimes may be missed.

My Blood Gets Too Thin with Warfarin

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Case: An 85-year-old man presented to the hospital with shortness of breath and coughing up blood. He had been admitted just 2 weeks prior for non-ST Segment Elevation Myocardial Infarction (NSTEMI), atrial fibrillation with rapid ventricular rate (RVR), bilateral pneumonia and was discharged on warfarin 4mg per day for atrial fibrillation and moxifloxacin for pneumonia. International normalized ratio (INR) on discharge was 1.3. After discharge, INR was monitored closely due to drug interaction between warfarin and moxifloxacin. He did well, but a few days later had to stop taking warfarin due to supratherapeutic INR. He then started developing progressive shortness of breath followed by nose bleeds and hemoptysis for which he presented in the TEC and was found to be hypoxic with Pa02 of 49.7 on 3L. INR was noted to be >9 and partial thromboplastin time (PTT) was 67.3. Direct visualization of nasopharynx with a rigid scope revealed areas of scabbing and old bleeding sites in the left anterior naris. Vitamin K and multiple units of fresh frozen plasma (FFP) were given; INR dropped to 1.6 but climbed up again requiring additional doses of vitamin K.

Patient had not taken more warfarin than recommended nor was there evidence of him taking super warfarin or brodifacoum. Brodifacoum levels were checked and were negative. Wafarin levels checked during his hospital stay revealed warfarin level of <1 despite an INR of 2. He was tested for VKORC1 and CYP450 2C9 and found to have genetic polymorphism involving both genes resulting in decreased production of an enzyme that metabolizes the active isomer of warfarin to inactive products and also decreased availability of vitamin K, making him very sensitive to warfarin.

Does Size Matter? Uncemented Total Hip Arthroplasty in Obese vs Non-Obese Patients: An 18- to 27-Year Follow-up Study

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Introduction: This study's purpose was to evaluate the incidence of aseptic loosening with use of an uncemented tapered femoral component in obese vs nonobese patients at 18 to 27 years (mean 23.5 years).

Methods: Between 1983 and 1987, 285 consecutive uncemented total hip arthroplasties were performed with use of a tapered stem. The patients were divided into 2 groups, obese and nonobese, as determined by their body mass index (BMI). There were 105 obese patients (119 hips, BMI ≥ 30) and 156 nonobese patients (166 hips, BMI < 30). The outcome of every femoral component with regard to stem fixation, revision, or retention was determined for all 285 hips. Complete follow-up was obtained on the 97 patients (111 hips) surviving a minimum of 18 years (range 18 to 27 years).

Results: Of the 119 hips in obese living and deceased patients, 1 stem (1%) had been revised for aseptic loosening and one was loose by radiographic criteria. In the 55 surviving hips, none had been revised for aseptic loosening and one was loose.

Of the 166 hips in nonobese living and deceased patients, none had been revised for aseptic loosening and one was loose by radiographic criteria. In the 56 surviving hips, none had been revised for aseptic loosening and one was loose. No significant difference between the 2 groups with regard to clinical outcome or perioperative complications was found.

Conclusion: Uncemented tapered stems provide excellent fixation in obese and nonobese patients out to 27 years.

Unraveling the Mystery: A Patient with Dancing Feet

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Introduction: Painful legs and moving toes (PLMT) syndrome is a rare medical disorder characterized by involuntary movements of the toes or the whole foot and pain in lower limbs.

Case: A 63-year-old man presented with complaints of involuntary movements in both legs over the last 8 to 10 years. These movements could be momentarily suppressed by voluntary action and did not persist during sleep. He also described a deep, aching, burning pain with fluctuating intensity in both legs. Electrodiagnostic, laboratory, and imaging studies were normal. Physical exam revealed semi-rhythmic flexion-extension and occasional abduction of the phalanges in both feet, especially the great toes, characteristic of PLMT syndrome.

Discussion: Spinal cord and cauda equina diseases, neuropathies, radiculopathies, drugs, and other systemic diseases are the main causes of this syndrome, although many cases still are idiopathic. The involuntary movements appeared bilaterally in the toes in our patient, which suggests that central reorganization (especially in the spinal level) is the cause of PLMT. Electromyogram (EMG) and nerve conduction studies have proven helpful in demonstrating spontaneous arrhythmic bursts of affected muscles and the underlying neuropathy in some patients.

Conclusion: Physicians should be aware of this rare debilitating condition. Though much progress has been made in elucidating its etiology, its exact mechanism still remains a mystery. It is important to consider PLMT in a patient with painful legs and/or restless leg syndrome without any significant history of neurological disease or trauma. Diagnosis is essentially clinical, and treatment is complex, including different combinations of drugs and invasive techniques with a poor outcome.

Lactic Acidosis and Confusion After a Fall

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Introduction: Confusion is a common reason for patients seeking urgent medical care. The causes are numerous with many that are potentially life-threatening, including toxic ingestions.

Case: A 52-year-old male presented with confusion and loss of coordination 24 hours after a fall with a binge drinking episode. During evaluation at an emergency department the evening of his fall, a head CT and basic metabolic panel were unremarkable. At breakfast his wife noted he was experiencing slowed and inappropriate speech and difficulty coordinating his gait. By the time he was admitted, his neurologic exam had become unremarkable. Initial laboratory evaluation showed an increase in creatinine to 1.11 from 0.76 mg/dl and a decrease in bicarbonate to 16 from 28 mg/dl the day prior. An arterial blood gas showed an anion gap metabolic acidosis with respiratory compensation. His serum lactate also was elevated markedly at 23 mmol/L. Urinalysis revealed occasional calcium oxalate crystals. Upon further questioning, the patient admitted to an attempted suicide prior to his fall by consuming 1 cup of ethylene glycol. Ethylene glycol level subsequently returned at 135 mmol/L. He was started on a fomepizole and bicarbonate drip and his anion gap acidosis resolved within 24 hours.

Discussion: Ethylene glycol is a widely available chemical found in industrial products. It is responsible for dozens of deaths in the United States annually. While ethylene glycol itself is relatively nontoxic, it is bro-

ken down into calcium oxalate and other harmful metabolites that can cause oliguric or anuric acute kidney injury. Usual presentations include development of mild central nervous system (CNS) effects such as inebriation and sedation, which are exacerbated with coingestion of ethanol. Other neurologic symptoms include cranial nerve palsies, tetany, and cerebral herniation in large doses. Renal manifestations are oliguria and hematuria due to crystal deposition. Workup in suspected poisonings should include basic chemistries, arterial blood gas, serum osmolality, and electrocardiogram (ECG). It also is important to rule out coingestion and establish the level of ingestion. Treatment in mild to moderate levels of ingestion consists of competitively inhibiting alcohol dehydrogenase and normalizing the patient's pH, with bicarbonate drip if necessary. More profound ingestions may require acute hemodialysis for the removal of this toxic and often lethal chemical.

A Case of Strongyloidiasis Unmasked by Corticosteroids

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Introduction: Most cases of strongyloidiasis in the United States are subclinical. They may occur seldom in debilitated or immunocompromised patients, and immunosuppressive agent recipients. We describe an unusual case of strongyloidiasis with intestinal and pulmonary manifestations in a Puerto Rican immigrant. His disease was unmasked after receiving high dose corticosteorids for pneumonitis.

Case: Our patient was a 75-year-old Puerto Rican man with multiple admissions over the past 3 months for progressive shortness of breath of uncertain etiology. He was diagnosed with asthma exacerbation and treated with corticosteroids, antibiotics, and bronchodilators. Prior to receiving corticosteroids, he had modest peripheral eosinophilia. Extensive workup led to a diagnosis with acute respiratory distress syndrome of unknown etiology with diffuse alveolar damage on biopsy. High-dose corticosteroids did not lead to clinical or radiological improvement. He started complaining of lower abdominal pain. Colonoscopy revealed superficial ulcerations and erythema in the ascending colon. Fusiform-shaped larva were noticed on the cecal biopsy. A positive repeated stool ova and parasite indicated *Strongyloides stercoralis.* A 2-day regimen of ivermectin was given, corticosteroids dose decreased. He returned 4 days later with progressive shortness of breath and was found to have pneumothorax and persistent diffuse bilateral lung infiltrates. His condition deteriorated with respiratory failure and failure to thrive. At that point, the patient and family opted to discontinue treatment. He was eventually discharged to hospice care and expired shortly after.

Discussion: Strongyloidiasis in immunocompetent hosts is asymptomatic, often limited to incidental finding of peripheral blood eosinophilia. However, in immunocompromised hosts, it often causes disseminated disease. Our patient most likely acquired the infection in Puerto Rico where he worked as a farmer. He was asymptomatic until he received high dose corticosteroids, which unmasked the diagnosis.

Spontaneous Upper Extremity Myonecrosis Secondary to Clostridium Septicum: Clue to Colonic Malignancy

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Introduction: Clostridium septicum can be differentiated from other *Clostridium* species by causing nontraumatic gas gangrene in tissues. Once culture is positive for *Clostridium septicum* in gangrenous tissue, suspicion of colorectal malignancy should be high. By hematogenous spread, *Clostridium septicum* will cause nontraumatic gas gangrene in immunocompromised patients with colorectal malignancy. The case report will portray a need for workup for underlying malignancy in the setting of spontanous nontraumatic gangrenous *Clostridium septicium* myonecrosis.

Case: A 49-year-old man with no significant past medical history presented to the emergency department (ED) with left-sided upper abdominal pain of 1 day duration with emesis, bloody diarrhea, right upper arm pain, and cramping. On physicial exam, he was diaphoretic, tachycardic, afebrile. Right upper arm, shoulder, and forearm and lateral chest wall were significant for swelling and mottling of skin with moderate tenderness and crepitence. X-ray showed extensive subcutanous emphysema. Antibiotics were started. Emergency surgical debridement and fasciotomy were performed. The arm was not salvagable and amputation was performed. Postoperatively, patient developed septic shock and was on mechanical ventilation. The culture from debridement was positive for *Clostridium septicum*. Abdominal CT did not show any masses. After resolution of septic shock and weaning from ventilation the patient underwent colonoscopy, which showed a 3-cm ascending colon mass; pathology report presented as tubulovillous ademona with intramural adenocarcinoma. Patient underwent hemicolectomy and was staged as IIIa (Dukes C).

Discussion: This case represents the importance of association between rare cases of *Clostridium septicum* nontraumatic gangrenous myonecrosis and occult malignancy. It emphasizes the need for extensive workup to exclude malignancy, especially colorectal cancer.

Recurrent, Reversible Acute Kidney Injury: Puzzles, Pointers, and the Allure of Internal Medicine

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Introduction: Sarcoid, noncaseating granulomatous interstitial nephritis (GIN) is an underrecognized entity of a well-known disease. Although first described in 1933 by Garland and Thomson, less than 50 case reports exist in literature. In 1 autopsy series, 20% of patients with sarcoidosis were noted to have GIN.

Case: We report a 76-year-old man who was referred for nonoliguric acute kidney injury

(AKI) (baseline creatinine of 1.3 mg/dL in September 2009 and 2.2 in September 2010) in the background of hypertension on fosinopril, atrial fibrillation on warfarin therapy, prostatic adenocarcinoma (prostate-specific antigen 11.42ng/mL, T2a Gleason grade 3+3/10), pulmonary sarcoidosis quiescent since 2006, and gastroesophageal reflux disease on omeprazole. Clinical exam was noncontributory.

In the absence of other abnormal laboratory parameters, failure to recover on withholding fosinopril, increasing creatinine 3.6 mg/dL, and expressed unwillingness to proceed with a kidney biopsy given warfarin use, the patient was advised to discontinue omeprazole and consider an empiric trial of prednisone for possible omeprazole-induced vs sarcoid interstitial nephritis. In 4 weeks, his renal indices recovered to 2.3 mg/dL and steroids were discontinued. However, he returned in 3 months with a recurrent episode of AKI (creatinine 5.6 mg/dL), evidence of mild hypercalcemia (10.7 mg/dL), normal intact parathyroid hormone (iPTH) and polyuria. The clinical pointer led to a kidney biopsy in the absence of pulmonary evidence of active sarcoidosis and a differential of metastatic prostatic carcinoma. It confirmed noncaseating granulomatous involvement, without acid-fast bacilli or evidence of vascular involvement. He was restarted on steroids, with dramatic improvement in renal indices (creatinine 2.3 mg/dL, Ca 8.8, iPTH 70 in 4 weeks of treatment).

Conclusion: In addition to highlighting all facets of sarcoidosis and renal GIN, this case demonstrates the relevance of recognizing the uncommon and sometimes subtle, extrathoracic pointer (hypercalcemia, past response to empiric steroid trial) of a relatively common disease. Furthermore, it underscores the allure of conundrums in medical practice that are not only challenging but also profoundly satisfying. This patient clearly had an eminently curable disease that was otherwise relentless and destined to saddle him with dialysis and its antecedent morbidity.

Papillary Thyroid Cancer in Monozygotic Twins

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Introduction: Numerous studies have demonstrated a slightly greater concordance for cancer in monozygotic twins. Also, in studies comparing familial with sporadic papillary thyroid cancer, some investigators have reported higher rates of multicentric tumors, lymph node metastasis, vascular invasion, and local invasion in familial forms. Two case reports published in 1955 and 1988 emphasized the role of genetic factors in twins with papillary thyroid cancer and we are reporting one more case diagnosed incidentally in a set of 37-year-old monozygotic twins.

Case: The first twin was referred to us by her OB/GYN for an incidentally discovered thyroid mass. Ultrasound-guided fine needle aspiration (FNA) cytology of the mass revealed papillary thyroid carcinoma; pathologic diagnosis at the time of total thyroidectomy indicated multifocal disease with metastases to local lymph nodes.

The second twin, healthy and completely asymptomatic, was referred to us by her sister for screening. Thyroid ultrasound showed bilateral small thyroid nodules, one of which was confirmed by FNA to be papillary carcinoma. Interestingly, she too was found to have metastatic disease at the time of surgery. Post ablation total body radioiodine scan detected persistent activity in the thyroid bed—not an uncommon finding. Within the following 6 months, the patient discovered new left neck lymphadenopathy. Lymph node mapping by ultrasound followed by FNA confirmed bilateral metastatic papillary carcinoma. The patient was referred for elective neck dissection; postoperative thyroglobulin level and imaging results are pending.

Discussion: Although the genetic basis for familial papillary thyroid cancer is yet to be completely understood, screening with ultrasound and FNA is warranted in monozygotic twins, as this report provides further evidence that the familial form of papillary carcinoma of the thyroid may exhibit aggressive behavior.

An All-Consuming Case

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Case: A 44-year-old man with a history of incarceration presented with 2 weeks of headache, fever, and night sweats. He reported progressive breathlessness, a 30-pound weight loss over 4 months, and photophobia. His admission temperature was 104°F. Chest x-ray demonstrated diffuse bilateral pulmonary interstitial nodular opacities that were concerning for miliary tuberculosis. His serum Quantiferon tuberculosis (TB) test was positive. Histoplasma, blastomyces, Pneumocystis carinii, cytomegalovirus (CMV) and HIV assays were negative. Bronchoscopy with bronchoalveolar lavage was performed, but sputum acid-fast bacilli smears were negative. Empiric antituberculosis chemotherapy was initiated with isoniazid, rifampin, pyrazinamide, and ethambutol. His headache and photophobia worsened. Cerebrospinal fluid (CSF)analysis showed 85 WBC with 9% lymphocytes, protein of 70mg/dL, glucose of 47mg/dL and a negative acid-fast bacillus (AFB) smear. Brain MRI showed innumerable supra and infratentorial 3-6 mm ring enhancing lesions with surrounding edema, consistent with tuberculomas. The final diagnosis was miliary tuberculosis with intracranial tuberculomas. Dexamethasone was added to his antituberculosis chemotherapy, with rapid resolution of his headache and fevers. He was discharged on directly observed therapy and prednisone. After discharge, his sputum cultures grew Mycobacterium tuberculosis.

CNS tuberculosis occurs in 1% of all TB cases in immunocompetent individuals. It carries a 15% to 40% mortality. Tuberculomas are extremely uncommon in the West, but they account for 20% to 30% of intracranial space occupying lesions in children in India and Asia. Classic CSF findings include low glucose and high protein and cell counts (with lymphocytic

predominance). Serial CSF AFB smears greatly improve the diagnostic sensitivity. TB CSF polymerase chain reaction (PCR) has 55% sensitivity and 95% specificity. Typically, isoniazid, rifampin, ethambutol, and pyrazinamide are used for 2 months, with isoniazid and rifampin being continued for a total of 12 months (18 months with tuberculomas). Multiple randomized control trials have demonstrated decreased mortality in patients who receive steroids in the treatment of TB meningitis.

A Tale of 2 Granulomas

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Introduction: Wegener's granulomatosis and blastomycosis are both granulomatous diseases that are difficult to diagnose, especially if both simultaneously affect the lung. Accurate diagnosis is important as it has therapeutic implications.

Case: We describe a 74-year-old man, ex-smoker, who presented with a 2-week history of bilateral conjunctivitis with left dacroadenitis. He was seen by ophthalmology 1 week prior to admission, when he was diagnosed with bilateral conjunctivitis and presumptively treated with antibacterial eye drops. However, the conjunctivitis worsened warranting a hospital admission, during which chest radiography demonstrated an area of lobar consolidation. The patient initially was treated for community-acquired pneumonia and bilateral conjunctivitis with IV antibiotics without improvement in either the lung consolidation or conjunctivitis/left dacroadenitis. Initial and repeat eye cultures were negative. Bronchoscopy with washing and biopsy of the lung lesion demonstrated numerous inflammatory cells without malignant cells. Subsequently, the patient underwent a CT-guided core biopsy with the same results aforementioned. He was continued on IV antibiotics without improvement. Given that his conjunctivitis also was not improving, biopsy of the lacrimal duct was performed and demonstrated granulomas. Subsequent, serologic testing was positive for cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and anti-proteinase 3 (PR3) antibodies. Also at this time, fungal culture from bronchoaveolar lavage grew a slow-growing mold, later identified as blastomycosis. Ultimately, the patient was diagnosed with both Wegener's granulomatosis without renal involvement and blastomycosis, and was treated for both with IV cyclophosphamide, prednisone, and itraconazole. Follow-up chest radiography showed improvement of the lung lesions with clinical improvement of the conjunctivitis.

Discussion: Wegener's granulomatosis and blastomycosis are 2 rare granulomatous diseases, one being an autoimmune disease process and the other a fungal infection. Diagnosis of either can be challenging, and diagnosing both at the same time can be a diagnostic dilemma. Part of diagnosing either is based on a good history. However, there can be atypical presentations, which require more focus on serology and histology.

VIGNETTES

Anaplasmosis as a Mimicker of Thrombotic Thrombocytopenic Purpura

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Introduction: Anaplasmosis is an illness endemic to the upper Midwest transmitted by *Ixodes scapularis.* It can mimic thrombotic thrombocytopenic purpura (TTP) insofar as it presents with thrombocytopenia, fevers, altered mental status, and acute kidney injury, but without microangiopathic hemolytic anemia. Early recognition in endemic areas can prompt rapid resolution and proper utilization of health care resources.

Case: A 59-year-old man with coronary artery disease (CAD) presented with 2 days of confusion, fevers, unsteady gait, and nonbloody diarrhea. Upon presentation, he was febrile, hypotensive, and disoriented. His exam was significant for the lack of hepatosplenomegaly, lymphadenopathy, or petechiae/purpura and was otherwise unremarkable. His complete blood cell count (CBC) revealed WBC 5.4, Hb 14.6 and platelets 35. His creatinine was 4.3 mg/dL indicating acute kidney injury and his lactate dehydrogenase (LDH) was 619 U/L. His smear revealed numerous burr cells but very few schistocytes. Hemolysis labs were negative. He was admitted to the intensive care unit (ICU), volume resuscitated, and started on broad-spectrum antibiotics. Given his constellation of symptoms, there was concern for TTP hemolytic uremic syndrome (HUS), so plasmapheresis was begun. His mental status began to improve before plasmapheresis was started however, and further history revealed that the patient bred horses in rural Wisconsin and admitted to multiple tick bites. Subsequently, *Anaplasma* and *Ehrlichia* DNA PCR tests, Lyme screen, and *Babesia* smear were collected. Doxycycline was started for empiric treatment of tick-borne illness. The patient's clinical condition, kidney function, and platelet count improved in the first 36 hours. *Anaplasma phagocytophilum* DNA returned positive 3 days later and his ADAMTS13 activity returned normal, further proving that he did indeed have anaplasmosis and not TTP-HUS. He required no further interventions and was discharged in stable condition with a 3-week course of doxycycline.

Discussion: Anaplasmosis and other tick-borne illnesses can present similarly to TTP-HUS, however there is no evidence of microangiopathic hemolytic anemia in the former. Tick-borne illnesses should be added to the differential depending on season and geographic location. This patient's initial improvement can be attributed to prompt treatment with antibiotics and not due to the plasmapheresis he received. Prompt recognition and treatment of anaplasmosis by internists and ED physicians can help avoid potentially unnecessary and expensive interventions such as plasma exchange, dialysis, and admission to the ICU.

An Unusual Case of Cardiac Tamponade

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Case: A 19-year-old man presented with a 1-week history of diffuse myalgias, arthralgias, subjective fevers, and initial sore throat. At the time of admission, he also had developed chest pain and dyspnea. Exam revealed a pericardial rub and sinus tachycardia. Lab findings included leukocytosis (WBC peak of 43.70, 91.3% granulocytes), anemia, and thrombocytopenia. Chest x-ray was significant for a left lower lobe (LLL) infiltrate. Transthoracic echocardiogram (TTE) revealed a trivial pericardial effusion without tamponade. Patient was started on NSAIDs for pericarditis and IV ceftriaxone and azithromycin for presumed community-acquired pneumonia.

On hospital day 2, he developed right upper quadrant (RUQ) pain, and an abdominal CT was significant for hepatosplenomegaly and retroperitoneal/mesenteric lymphadenopathy. On hospital day 3, he developed increased chest pain and dyspnea and repeat TTE was suggestive of impending tamponade. He was intubated secondary to acute respiratory failure, and an emergent pericardial window was placed. Chest x-ray revealed diffuse infiltrates. Bronchoscopy/BAL were unrevealing. The patient then developed a diffuse maculopapular rash and became febrile to 102.4°F with prior low-grade fevers. Infectious disease was consulted and extensive work-up was completed with negative cultures and testing for HIV, Epstein-Barr virus, CMV, influenza, enterovirus/coxsackie, adenovirus, parvovirus, Lyme, anaplasma/ehrlichia/rickettsial panel, tularemia, chlamydia, brucella, fungal antibody panel. Anti-histoplasma Ab was positive. Itraconazole was initiated.

Due to a largely negative infectious work-up, lack of clinical improvement, and concern for adult-onset Still's disease (AOSD), rheumatology was consulted. Ordered labs all were negative with the exception of a significantly elevated ferritin of 11,888 ng/ml, C-reactive protein (CRP) 29.5 mg/dl, and erythrocyte sedimentation rate (ESR) 83 mm/hour. Patient was started on high-dose steroids and began to clinically improve. He was discharged on prednisone and itraconazole. The working diagnosis was AOSD vs disseminated histoplasmosis. Follow-up testing for histoplasma Ab was negative. The patient's final diagnosis was AOSD.

Discussion: Adult-onset Still's disease is a rare inflammatory disorder with yet unclear etiology. Diagnosis may be guided by the Yamaguchi criteria. The major criteria include intermittent fever of at least 39°C for > 1 week, arthralgias for > 2 weeks, characteristic skin rash, leukocytosis with > 80% granulocytes. The minor criteria include sore throat, lymphadenopathy, hepatosplenomegaly, abnormal liver function tests, and negative antinuclear antibody (ANA)/ rheumatoid factor (RF). Significantly elevated ferritin levels also are seen in up to 70% of patients with AOSD.

Diabetic Myonecrosis: Diagnostic and Therapeutic Pitfalls

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Introduction: Diabetes and consequent end organ damage of retinopathy, nephropathy, and neuropathy are well recognized. However, Diabetic Myonecrosis (DMN), a relatively rare, potentially life- and limb-threatening complication is underrecognized and often misdiagnosed.

Case: A 43-year-old morbidly obese man with poorly controlled diabetes (HbA1C 10.8% - 17.5%) presented with a subacute history of a very painful thigh of approximately 10 to 12 weeks duration. He denied any history of trauma, fever, or chills. Musculoskeletal exam revealed a profoundly swollen, tender distal right thigh without skin breakdown, erythema, or crepitus, and a range of motion limited by pain. Anterior and posterior thigh compartments were soft without evidence of elevated compartment pressures. Peripheral pulses were palpable, reflexes mildly diminished, and a left diabetic foot ulcer was noted. Labs revealed anemia (7.9g/dL), mild leukocytosis, and elevated CRP (19.3 mg/dL). A Doppler ultrasound ruled out deep venous thrombosis. A presumptive diagnosis of cellulitis with edema was made.

Four days later, in the absence of objective improvement and new onset acute kidney injury (AKI, creatinine 2.6 mg/dL), he was noted retrospectively to have subacute persistently elevated creatinine kinase ranging from 564 to 369 IU/L). A urinalysis revealed diabetic proteinuria (2.54 g/mg) with a benign sediment. A diagnosis of DMN was made and confirmed by MRI with gadolinium. It revealed profound edema in the subcutaneous fat, perifascial, multifocal enhancement of the quadriceps and adductor muscles, in addition to an extensive area of absent enhancement within the right vastus medialis suggesting muscle necrosis. He subsequently was dialyzed temporarily to remove gadolinium. A muscle biopsy was consciously withheld to avoid infection. Conservative therapy with bed rest, analgesia, and short-term immobilization resulted in improvement. Most recent creatine kinase (CK) was 88 U/L.

Conclusion: Heightened awareness for the occurrence of DMN as a complication of diabetes so frequently observed in clinical practice would facilitate prompt recognition, avoid invasive diagnostic interventions, and prevent iatrogenic morbidity. Institution of conservative management may in all likelihood culminate in improved outcomes. This case also highlights the role of MRI as a diagnostic tool and the role for prophylactic temporary hemodialysis to decrease risk for nephrogenic systemic fibrosis in the background of gadolinium exposure and AKI.

Myxedema Madness, Stertor, and Rhabdomyolysis

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Introduction: The clinical presentation of thyroid hormone deficiency is diverse, subtle, and nonspecific. We describe a case of

a patient with myxedema presenting with unusual clinical features of stertor and muffled voice.

Case: A 59-year-old man presented with 1-month history of shortness of breath, stertor, and 2 days of visual hallucinations. He was diagnosed with hypothyroidism 4 days prior to presentation and was prescribed levothyroxine 100 mcg once daily. Physical examination showed temperature 97.6°F, blood pressure 144/80 mm/Hg and pulse 76 bpm. He was alert and oriented with stertorous breathing pattern. His voice was muffled and skin was thick, coarse, and dry. There were no palpable thyroid nodules. Lower extremities showed nonpitting pretibial edema.

Emergency fiberoptic laryngoscope was performed showing upper airway narrowing with mucosal thickening. Laboratory studies were significant for thyrotropin (TSH) 54.69 uIU/ml, CK 21963 U/L, aspartate aminotransferase 625 U/L, sodium 106 mmol/L, and chloride 75 mmol/L. Ultrasound of neck showed diffuse, multinodular goiter. Treatment was initiated with nasopharyngeal airway, continuous positive airway pressure (CPAP), hypertonic saline 3%, IV, hydrocortisone, and thyroid hormone replacement. Hydrocortisone was discontinued when the results of cortrosyn stimulation test showed normal response.

Discussion: Our case highlights the multisystem clinical manifestations of myxedema. Stertor refers to heavy snoring sound heard during respiration. Stertor and muffled voice, as seen in patients with myxedema, are due to the deposition of connective tissue component in pharyngeal tissue causing airway obstruction. Psychiatric manifestations include cognitive dysfunction, affective disorders, psychotic features, or so-called myxedema madness. Failure to recognize and promptly initiate therapy with thyroid hormone replacement is associated with mortality as high as 60%. Hydrocortisone should be administered until the results of the cortisol levels are known since failure to treat in the presence of adrenal insufficiency could result in adrenal crisis.

Pulmonary Nodules and Fever in an Immunosuppressed Patient

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Introduction: Histoplasmosis is a fungal infection that presents as a flu-like illness. It is typically self-limited in healthy patients and resolves without intervention. In immunocompromised patients, histoplasmosis is more likely to progress to fulminant disease without intervention. The nonspecific presentation of histoplasmosis in immunocompromised patients challenges clinicians by fostering a broad differential diagnosis. The potential for early progression to fulminant disease in immunocompromised patients lends to the importance of an aggressive work-up and early treatment.

Case: A 73-year-old white woman with a 30-year history of Crohn's disease presented to her internist with a 3-day history of intermittent fevers, chills, night sweats, weakness, and arthalgias. The patient did not have any respiratory symptoms upon presentation, however, her history was significant for a productive cough that spontaneously resolved 1 week prior to developing fevers. The patient's medication regimen included nightly total parenteral nutrition (TPN) infusions, infliximab, rifaximin, and moxifloxacin. Initial ambulatory work-up was unremarkable for an infectious or neoplastic etiology. On subsequent ambulatory work-up, chest CT revealed multiple pulmonary nodules with mediastinal and hilar lymphadenopathy. The patient was admitted and underwent bronchoscopy, which did not yield a diagnosis. The patient's symptoms continued to progress. On hospital day 5, mediastinoscopy yielded specimens containing Histoplasma capsulatum. Subsequent serology and antigen studies were negative suggesting nondisseminated disease. The patient was treated with fluconazole and her symptoms resolved after 7 days. Serial CT scans at 14 and 24 weeks showed a favorable response to treatment with a reduction in the size and number of pulmonary nodules.

Discussion: Histoplasma capsulatum is a dimorphic fungi often present in soil. It is endemic to the Ohio and Mississippi River valleys. Infection occurs through direct inhalation of microcondidia. Primary manifestations depend on the degree of exposure and the immune status of the host. Approximately 10% of immunocompetent patients develop a self-limited flu-like illness characterized by fevers, chills, night sweats, cough, and myalgias. Chronic pulmonary and disseminated infections occur most frequently in immunocompromised patients. Serology and antigen studies are highly sensitive and specific for differentiating between isolated pulmonary infections and disseminated disease. Effective treatment of progressive or chronic infections includes amphotericin B, fluconazole, and itraconazole. Immunocompromised patients may require lifelong treatment to prevent recurrence.

Diagnosed Skin Deep

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Introduction: Pyoderma gangrenosum (PG) is most often associated with inflammatory bowel disease (IBD); however, rare subtypes may be associated with underlying malignancy.

Case: A 64-year-old white man presented from an outside facility with a 6-week history of a warfarin and catheter-directed thrombolysis-resistant deep vein thrombosis and a 2-week history of two progressively enlarging ulcerations on his left leg. These lesions were initially dime-sized, but by the time of transfer, had progressed to diameters of 20 cm and 25 cm. His physical examination was significant for left lower extremity edema and exquisite tenderness. Skin biopsy showed a dense, diffuse, neutrophilic infiltrate in the superficial and deep dermis consistent with PG. Tissue cultures were negative for bacterial and fungal elements. Initial labs were significant for an isolated anemia with hemoglobin of 8.0 g/dL, which had been stable throughout his hospitalization. However, repeat assay revealed pancytopenia with WBC 4.6 x 10^3/uL, hemoglobin

6.9 g/dL, and platelets 158 x 10^3/uL. Blood smear revealed 2% unclassifiable cells. In the context of pancytopenia and unclassifiable cells on the peripheral smear, a bone marrow biopsy was obtained to evaluate for myeloid malignancy. The aspirate contained 33% blasts with a hypercellular core biopsy, which confirmed the diagnosis of acute myelogenous leukemia (AML). The patient was started on treatment with oral prednisone, but his hospital course was complicated by an episode of atrial fibrillation with rapid ventricular response and acute kidney injury. Due to these comorbid conditions, he was not a candidate for induction chemotherapy, and after initiating hemodialysis, he developed acute respiratory failure. Following a goal-setting discussion, his family chose to proceed with comfort measures only. The patient died on hospital day 18.

Discussion: PG is a rare disease often associated with inflammatory bowel disease. However, it has been described in other disorders, including acute myelogenous leukemia (AML). PG primarily affects young to middle-aged adults, but it has been described in all age groups. The type of PG described in patients with underlying hematological malignancy is usually the superficial bullous subtype of PG. It appears as an aggressive, painful, necrotic lesion with superficial bullae that break down to form an ulcerated lesion with undermined edges. The surrounding skin has pathognomonic violaceous borders. The course of the skin lesion parallels the hematological disorder. The presence of PG is an ominous sign with one study citing 23 cases with only 4 patients living past 8 months. Treatment usually consists of steroids for the PG and treatment of the underlying malignancy or disorder. As described above, outcomes generally are poor when associated with PG.

Curse of the Caribbean

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Case: A 74-year-old woman with rheumatoid arthritis treated with hydroxychloroquine developed 1 episode of mild gastroenteritis of 1 to 2 days duration while on a week-long vacation in the Caribbean. Six weeks later, the patient was admitted to a local hospital with gradual worsening of her chronic back pain, generalized weakness, frequent falls, and episodes of confusion. She was afebrile with stable vitals and had marked back pain with movement. Palpation tenderness was present in the paraspinal region of her lower back. Head CT and x-ray of lumbar spine was unrevealing. Blood cultures grew *Salmonella* serotype Enteritidis. The patient received IV levofloxacin for 5 days, and with clinical improvement, she was discharged with an additional 5 days of oral levofloxacin.

Three weeks later, the patient was readmitted to the same hospital with complaints of persisting back pain, weakness, and confusion. She had a fever of 104.2°F with midline lumbar tenderness. After transfer to our hospital for further care, we performed an MRI of the spine that showed L4-L5 diskitis. Blood cultures and disc space aspirate cultures grew *S. enteritidis*. Abdominal CT showed a 2-cm saccular mycotic aneurysm of the distal abdominal aorta. While on ceftriaxone, patient underwent aneurysmectomy with aortic reconstruction using autologous spiral saphenous vein graft. Tissue culture from the resected aneurysm also grew *S. enteritidis.* She was continued on ceftriaxone for a total of 6 weeks. Her pain improved and she was doing well when seen 2 months later at follow-up in clinic.

Discussion: Mycotic aneurysm is a rare but serious complication of nontyphoidal *salmonella* bacteremia, occurring most commonly in the abdominal aorta. This case demonstrates the importance of clinicians' awareness that adults with a relapse of *salmonella* sepsis often have a serious endovascular infection. This risk is increased in patients above 50 years of age with atherosclerosis. Anti-*salmonella* antimicrobial therapy should be started and a CT or MRI with contrast should be performed on an emergency basis. Following diagnosis, surgical resection of the aneurysm with in situ graft revascularization, the procedure of choice, should be done as soon as possible. Postoperative antimicrobial therapy for 6 to 8 weeks based on ESR and clinical response is recommended.

Early Lung Cancer Presenting as Hoarseness

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Introduction: Hoarseness is a symptom with numerous causes, including malignancy. Rapid determination of its source is necessary to identify serious but potentially curable etiologies.

Case: A 42-year-old white man with a 25-pack-year smoking history presented with a complaint of 4 weeks of hoarseness. On further interview, the patient also had dyspnea, productive cough without hemoptysis, and weight loss of 50 pounds over 3 months. Besides mild tachypnea and anxious appearance, the patient's vital signs and physical exam were normal. Similarly, his complete blood count and basic chemistry panel were within normal range, and a urine drug screen was negative. His chest x-ray revealed densities superimposed over the left upper lobe, thought to represent either a deformity of the left 3rd rib or a pneumonic infiltrate. Chest CT with contrast was obtained to further evaluate this finding and revealed a 2.8-cm left upper lobe mass accompanied by ipsilateral hilar adenopathy involving the aorto-pulmonary window (through which the left recurrent laryngeal nerve courses). In follow-up, bronchoscopy with biopsy showed non-small cell lung cancer, ultimately staged as T2N1M0 (IIB). He was thereafter scheduled for video-assisted thorascopic surgery-based resection of the neoplasm.

Discussion: Lung cancer remains the primary cause of cancer death in the industrialized world, and diagnosis at an earlier stage is more amenable to potentially curative surgical intervention. In the primary care setting, historical details shown to be independently associated with a diagnosis of lung cancer include hemoptysis, dyspnea, cough, anorexia, weight loss, and cigarette use. Hoarseness is less often associated with pulmonary neoplasia but

still caused by extra-laryngeal malignancy 13.5% of the time, and by lung cancer most often among these (6.6%). Therefore, given the grave nature of lung cancer, it is important to consider it as an etiology when assessing the complaint of hoarseness, especially when accompanied by the listed independently associated symptoms. Although the primary diagnostic modality in evaluating hoarseness is laryngoscopy, neck and chest CT should be considered when laryngoscopy is normal or identifies vocal cord paralysis of uncertain cause.

Recurrent Acute Myocardial Infarction in a Patient with Immune Thrombocytopenic Purpura

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Case: A 58-year-old white woman with medical history of immune thrombocytopenic purpura (ITP) (but no known coronary artery disease history) was admitted with shortness of breath and chest pain. ECG and cardiac biomarkers demonstrated an acute ST-elevation myocardial infarction (STEMI). Coronary angiography was performed urgently and revealed thrombosis in the mid-left anterior descending (LAD). Aspiration thrombectomy of the LAD was performed successfully. No lesions were detected in the LAD or other coronary arteries that required stenting. Heparin, eptifibatide, aspirin, and clopidogrel were instituted prior to thrombectomy. The patient developed recurrent chest pain with new ST-segment elevations and cardiogenic shock in the following 18 hours. Another coronary angiogram showed repeat extensive thrombosis of the LAD with distal embolization. Large clot burden was painstakingly extracted but distal perfusion remained suboptimal. Hypercoagulable state was suspected due to recurrent thrombosis without anatomical lesions, and extensive coagulation work-up was done that turned out negative. The patient was placed on anticoagulation, aspirin, and clopidogrel without bleeding complications or thrombocytopenia. To reduce the risk of thrombocytopenia bivalirudin instead of glycoprotein IIb/IIIa antagonists were used for the second myocardial infarction. Prednisone was continued for maintenance treatment of ITP.

Discussion: ITP predominantly causes bleeding but also may be associated with thrombotic events. The mechanism of arterial thrombosis in ITP patients is still unclear, but several hypotheses exist. Thrombolytic therapy is contraindicated in acute myocardial infarction in ITP patients. Primary percutaneous coronary intervention (PCI) can be safe in this setting. During and post PCI procedure, glycoprotien IIb/IIIa inhibitors and anticoagulation should be used cautiously. Dual antiplatelet therapy can be well tolerated in some patients. Another consideration that needs to be pointed out is that the major goal for treatment of ITP is to provide a safe platelet count rather than correcting the platelet count to normal levels.

A Case of Atypical Adenoma and Papillary Thyroid Carcinoma

Nihad Yasmin, John C. O'Horo; Aurora Health Care Internal Medicine Residency Program, Aurora Sinai Medical Center, Milwaukee, Wis

Introduction: Atypical parathyroid adenoma is a rare etiology for primary hyperparathyroidism. These neoplasms share some histologic characteristics with parathyroid cancer but do not meet the rigorous criteria of cancer. One such case and a discussion of the differential diagnosis of primary hyperparathyroidism are presented here.

Case: A 79-year-old woman with a history of cholelithiasis was brought to the ED for generalized weakness following a flight. Associated symptoms included weight loss, constipation, and decreased mental acuity. Physical examination revealed significant muscle wasting of the thenar eminence and a thyroid nodule. Lab work was significant for calcium of 18.0 and PTH 1558. Initially, she was treated with pamidronate and hydration. Ultrasound of the thyroid showed mass in the left thyroid lobe and a soft tissue lesion interposed between the superior left thyroid lobe and common carotid artery. Further imaging revealed the nodule had intense sestamibi and mild iodine activity, suggestive of a thyroid cancer with a closely associated parathyroid neoplasm. She received definitive therapy with total thyroidectomy, node dissection, and parathyroidectomy. Histopathology showed papillary thyroid carcinoma of follicular variant, and an atypical parathyroid adenoma. The parathyroid mass did not clearly fit criteria for malignancy, but the local invasion and presence of coagulative tumor necrosis led to treating this as a parathyroid carcinoma. Patient tolerated the surgery well and was discharged from the hospital on calcitriol and close follow-up.

Discussion: Parathyroid carcinoma, atypical parathyroid adenoma, and parathyromatosis account for about 2% of cases of primary hyperparathyroidism (PHPT). This patient's nonspecific clinical course, and extremely elevated serum calcium and parathormone are typical findings of parathyroid carcinoma. The concomitant finding of associated thyroid cancer is very rare, only having been reported 5 times before. The long-term treatment plan will necessarily involve close surveillance for recurrence as the patient does not clearly need radio or chemotherapy.

Advance Care Planning Conversations Can Be Difficult, But Essential

George M. Lange, MD, FACP

Talking about dying—indeed planning for it—is difficult for most people. As a result, far too many of us don't do it. During the past year my goal as president of the Wisconsin Medical Society (Society), has been to increase awareness about the importance of end-of-life conversations. I believe it's essential that everyone talk with loved ones about their health care wishes in the event that they are unable to make those decisions themselves. Then, we need to complete an advance directive and share that information with our physician.

Wisconsin law recognizes 2 forms of advance directives: Power of Attorney (POA) for Health Care and Declaration to Physicians (Wisconsin living will).

According to statistics from the State Bar of Wisconsin, an estimated 80% of Wisconsin adults—including 50% of those with severe or terminal illnesses—have not completed an advance directive to document their preferences about issues surrounding end-of-life decisions.[1]

These statistics are similar to those nationwide. According to a 2006 report from the Pew Research Center, just 29% of those surveyed (N=1500) had a living will, and even fewer had taken steps to appoint a health care power of attorney.[2]

Doctors, on the other hand, are more likely to communicate their wishes. In a recent Wall Street Journal article titled *Why Doctors Die Differently*,[3] Dr Ken Murray cites a survey of 765 doctors, 64% of whom had created an advance directive—a number far above the national average.[3]

I surveyed a number of physicians as well, with similar results. Of the 1165 physicians who responded, 61% said they have completed an advance directive, and 26% indicated they plan to do so in the next 12 months.

So why are doctors ahead of their patients when it comes to advance care planning?

In his article, Dr Murray said, "Doctors don't want to die any more than anyone else does. But they usually have talked about the limits of modern medicine with their families. They want to make sure that, when the time comes, no heroic measures are taken. During their last moments, they know, for instance, that they don't want someone breaking their ribs by performing cardiopulmonary resuscitation."[3]

Generally speaking, I agree. Last year during its Annual Meeting, the Society screened the film "Consider the Conversation—A Documentary on a Taboo Subject." This film, which has aired on public television stations across the country, explores society's perceptions about end-of-life issues. It points out that dying often doesn't occur in the same way it did in previous generations: with many family members and neighbors gathered together, taking care of their loved one, at home. Because of advances in medical technology and families scattered across the country, death often occurs in the hospital even though what many people say they want at the end of their lives is to die at home surrounded by their loved ones.

As a primary care physician who is privi-

> Advance care planning is not about giving up hope or trying to put limits on the care a person receives. … Rather, it's about having a conversation with loved ones about what is important to us so our wishes can be honored when the time comes—in a year or 20 years.

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leged to care for a significant number of elderly patients, I've seen too often situations in which a patient experiences a stroke or heart attack, or the progression of cancer or another medical condition leaves them unable to communicate. Family members and loved ones agonize because they simply don't know what treatment their mother or husband or grandparent or son would want. Serving as a "surrogate decision-maker" is extremely stressful. Would their loved one choose aggressive treatment to prolong their life? Would they refuse a feeding tube, intubation or other medical options? Or would they choose something they feel is in the middle?

Advance care planning is not about giving up hope or trying to put limits on the care a person receives. Indeed, it can be used to ensure that every possible medical intervention is deployed. Rather, it's about having a conversation with loved ones about what is important to us so our wishes can be honored when the time comes—in a year or 20 years.

Hopefully, by now you are wondering what you can do to help your family, friends, and patients have a conversation about their advance care planning and take action. Consider the following:

- If you haven't done so already, I suggest you start by sharing your wishes with your loved ones and completing your own health care POA document. Then work with medical staff at your hospital or clinic to encourage nurses, case managers, and social workers to do the same.
- When you do a complete evaluation or clear a patient for elective surgery, strongly encourage your patient to have a conversation with his or her loved ones and complete their own health care POA.
- Ask your medical school to encourage students to complete a health care POA as part of their training.
- Ask to speak about the importance of advance care planning at your hospital, clinic, place of worship, or a local community group. (The Wisconsin Medical Society has resources available that can assist you.)

Advance care planning shouldn't be a taboo subject. Instead, it is an opportunity to empower people to advocate for the care they want for themselves as their life comes to an end. As a dear friend once said to me, "None of us are getting out of here alive."

As physicians, we can empower patients by helping them understand the importance of communicating their wishes to their loved ones. It's difficult to start a conversation about the end of life, but it is critical so our choices are honored by those who care for us.

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Marc K. Drezner, MD

Robert N. Golden, MD

Transforming the Research Environment and Culture for the Betterment of Health in Wisconsin

Marc K. Drezner, MD; Robert N. Golden, MD

A fundamental transformation of the research culture and environment is taking place in Wisconsin, and it will eventually elevate the health of the people of the Badger State in a dramatic way. The transformation—which ensures that research moves rapidly from the university to doctors' offices, clinics, hospitals and county health departments—originated in the Institute for Clinical and Translational Research (ICTR) at the University of Wisconsin-Madison. ICTR was created 5 years ago, when UW-Madison's health sciences schools, in partnership with Marshfield Clinic, won a highly competitive $41.5 million Clinical and Translational Science Award (CTSA) from the National Institutes of Health (NIH). The grant is one of the largest ever awarded to the UW School of Medicine and Public Health.

The CTSA program grew out of the vision of Elias Zerhouni, MD, Director of the NIH from 2002 to 2008. He envisioned a consortium of universities that would speed the translation of laboratory discoveries into treatments for patients, engage communities in clinical research efforts, and train a new generation of clinical and translational researchers.

The ultimate goal of ICTR is to achieve significant improvements in human health, with particular emphasis on lowering the impact of those diseases that are most prevalent in Wisconsin populations. We are experiencing remarkable success in building the foundation for this important goal by focusing on communities and investigators. We are nurturing biomedical and behavioral scientists who want to engage in community research, and we are providing them with training and resources to pursue their community research passions. At the same time, we are creating strong, lasting partnerships with a network of statewide communities and community organizations that are eager to identify research priorities that they believe will lead to better health outcomes in their neighborhoods.

Through an excellent Research Education and Career Development program, ICTR-supported young faculty members are developing their abilities to conduct type 1 translational research, which involves the movement of basic laboratory science into controlled clinical trials, and type 2 translational research, which involves community- and population-based studies. The number of UW faculty members now pursuing type 2 translational research, in which researchers collaborate closely with communities and/or community organizations, has nearly tripled in the past 5 years. And the number of these highly trained and productive interdisciplinary researchers continues to grow.

In addition to promoting the development of translational investigators, ICTR funds promising pilot research projects. In its first 5 years, it allocated $4,837,000 to more than 100 such projects. The ICTR-funded studies

The ultimate goal of ICTR is to achieve significant improvements in human health, with particular emphasis on lowering the impact of those diseases that are most prevalent in Wisconsin populations.

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resulted in the publication of 40 articles in peer-reviewed journals. These pilot studies in turn led to more than $21.5 million in federal grants, a remarkable "return on investment." The impact of these research projects will extend far beyond the communities that participated in the studies, as the findings can be applied throughout the state. A few examples of ICTR-sponsored pilot projects include development of a tool for diabetes risk assessment in children, testing a psycho-education intervention for families of adolescents with autism spectrum disorder, improving work ability among breast cancer survivors, treating tobacco dependence through community agencies, and expanding primary care treatment of chronic kidney disease.

ICTR also is dedicated to addressing health disparities across Wisconsin. We successfully competed for an additional NIH award that has allowed us to create the Collaborative Center for Health Equity (CCHE), which is now an ICTR core activity. CCHE concentrates on engaging with under-represented communities, funding research, and fostering the development of scholars—all aimed at eliminating health inequities.

One example is a healthy lifestyles program based at the Great Lakes Intertribal Council and other Wisconsin native American communities. The goal is to reduce the high rates of childhood obesity that can lead to related diseases during adulthood. Another planned project is a new partnership with the Lindsay Heights Community, a 110-square-block neighborhood in central-city Milwaukee. Lindsay Heights is planning for the construction of an Innovation and Wellness Commons structure that will serve as a gathering place for community groups and academic partners to offer educational programs, health activities, and related community-based research.

Establishing and maintaining long-term, mutually respectful, and trusting partnerships is essential to the success of these projects and all ICTR programs. Community engagement is crucial for all of what we do. ICTR staff based throughout the state support an array of community networks, including the Community Health Connections, the Wisconsin Network for Health Research (WiNHR), the Wisconsin Research and Education Network (WREN), Wisconsin Public Health Practice-Based Research Network and Marshfield Center for Community Outreach. Our 5 research ambassadors also work with local communities to establish bidirectional communication, which sets the stage for a collaborative approach in the development of research ideas and priority setting.

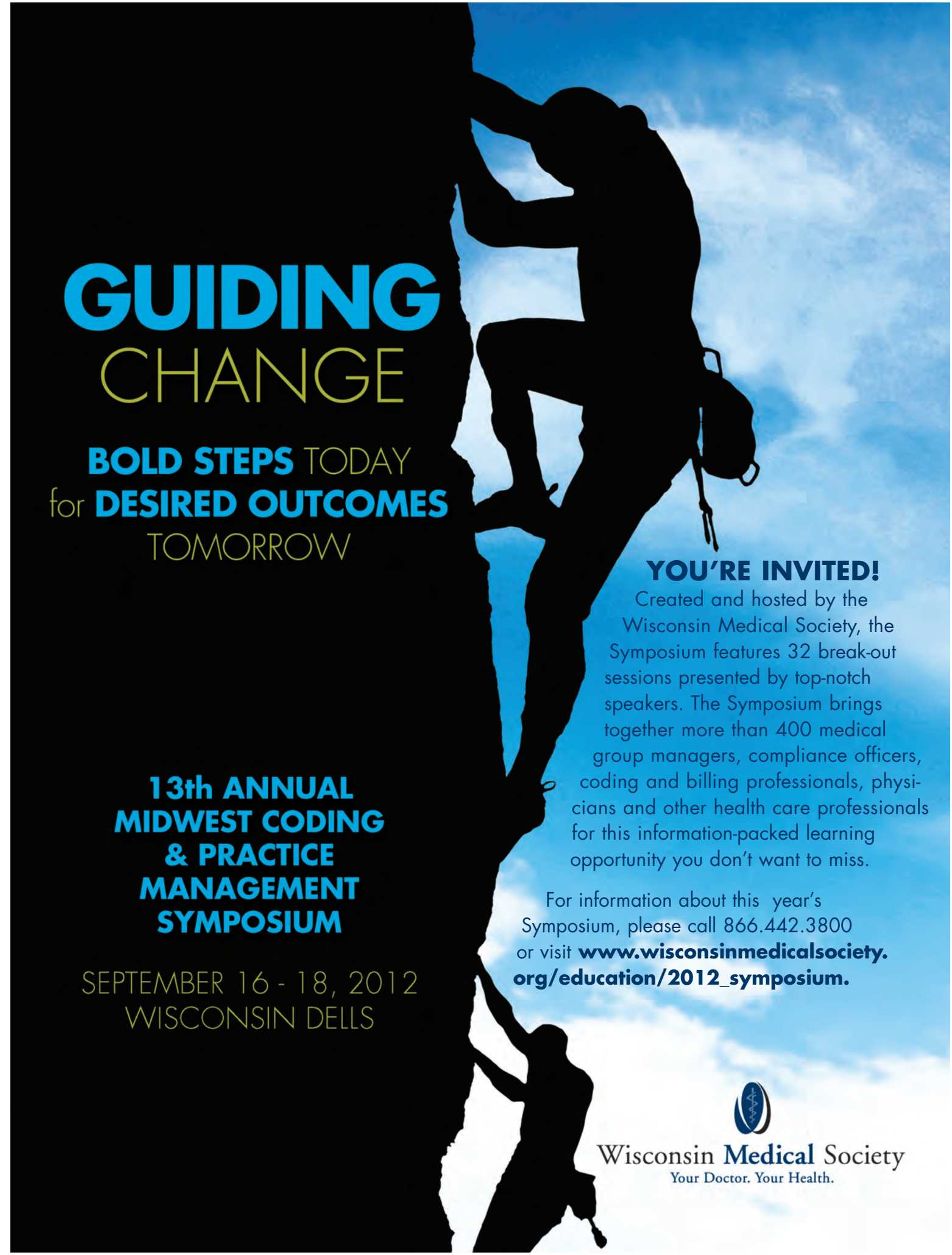
Community engagement also embraces health services research—which improves the processes by which health care is delivered. Several ICTR-funded projects with explicit dissemination or implementation activities have directly changed clinical practice, community health programs, and/or health policy. For example, an ICTR project that investigated barriers to colorectal screening led a local insurance provider to expand client benefits to include a more patient-friendly preparation for colonoscopy screening. Some 90,000 individuals were affected.

In addition to establishing relationships between community and academic partners, ICTR has offered educational and training activities to develop community partners' skills and has collaborated with community organizations to obtain grants totaling $27 million for the support of new type 2 translational research linked directly to community engagement.

ICTR provides centralized infrastructure support to our community partners. For example, we offer electronic data warehousing capabilities, biomedical informatics expertise, and an institutional review board dedicated primarily to type 2 translational research proposals. We also have an extensive video library, periodical e-newsletters, and an active website. It all is designed to be "user friendly" for all investigators pursuing community-based translational research in Wisconsin.

We hope to expand the scope of our influence even further with the creation of an Upper Midwest Consortium that would unite ICTR with the CTSAs at the University of Minnesota, the Medical College of Wisconsin, Northwestern University, and perhaps others. Pooling and sharing our resources and expertise can yield great synergies.

Although an enormous amount of effort has been dedicated to this transformation of the Wisconsin research culture and environment, much remains on our "to do" list. Fortunately, our federal grant has been renewed for another 5-year round of funding, a testimonial to the fact that we have accomplished a great deal in the past 5 years. With a clear set of strategic goals and outstanding institutional support, ICTR is well positioned for more success in the future. We hope to expand our collaborations with central-city minority and rural populations; build new statewide research networks that will focus on aging, obesity and public health; expand training opportunities for investigators and communities; and increase our work in disseminating and implementing the results of our research. If you have not yet observed the impact of these efforts, we hope that you will in the near future.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