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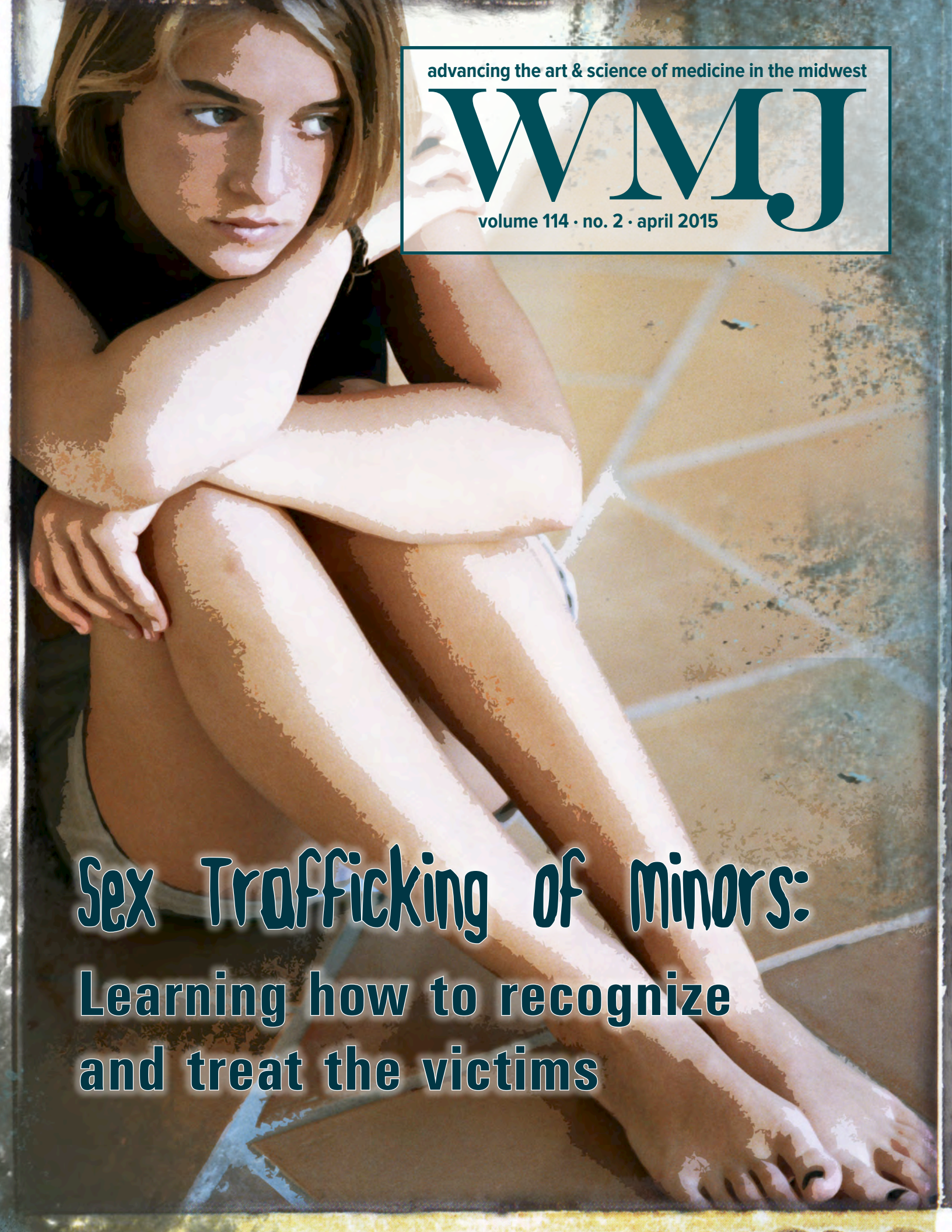

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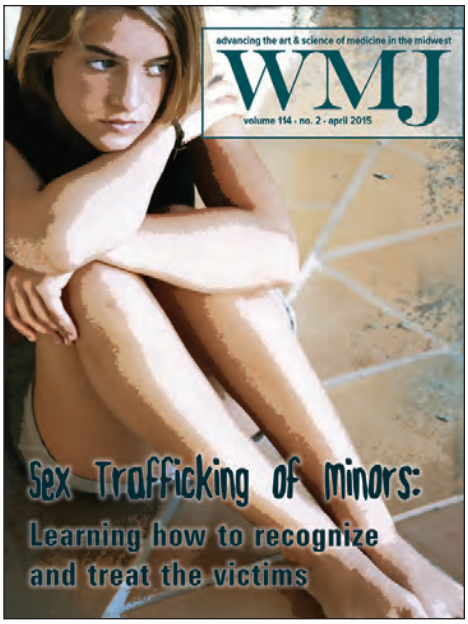

COVER THEME
Sex Trafficking of Minors: Learning how to recognize and treat the victims

Improved community awareness of sex trafficking of minors has sparked increased awareness among physicians and other health care professionals. However, many continue to underestimate the problem locally and have little confidence in their ability to identify and assist victims. A report in this issue of *WMJ* takes a closer look at the issue and presents guidelines for the medical care of victims.

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Mary Kay Adams-Edgette

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I Wonder . . .

Karl H. Doege, Medical Editor; Mr. J.G. Crownhart, Managing Editor;
Miss Dorothy Cirdland, Assistant Editor

Editor's note: The following editorial was published in WMJ, *Volume 39, p. 200, March 1940.*

Despite the fact it is often said "a prophet is not without honour, save in his own country and in his own house," our State has had many great authors whose writings deserve the recognition they received from the people of Wisconsin. One such is Ray Standard Baker who used the pen name, David Grayson, to write his "Adventures in Understanding."

In these days when the physician on the firing line sometimes feels a sense of inadequacy in combating with effectiveness the constant bombardment by those who are willing to make medicine the plaything of politics rather than the handmaiden of science and the servant of the people, it is particularly apropos that we recall what David Grayson had to say about just this situation; namely—

> I wonder if ever you change human beings with arguments alone: either by peppering them with little sharp facts or by blowing them up with great guns of truth. You scare 'em, but do you change 'em? I wonder if ever you make any real difference in human beings without understanding them and loving them. For when you argue with a man (how much more with a woman), you are somehow trying to pull him down and make him less (and yourself more); but when you try to understand him, when you like him, how eager is he then to know the truth you have; and you add to him in some strange way, you make him more than he was before; and at the same time, and that is the sheer magic of it, you yourself become more.

Who understands his people and their problems better than the family physician who lives with them because he loves them? *He* can give them the understanding they seek and need in this day of statistical attacks that too frequently conceal rather than reveal the real truth.

Asking Hard Questions

John J. Frey III, MD, Medical Editor

One reason that generalist physicians of all types are able to ask hard questions of our patients is that we have committed ourselves to being with them after the answers to those questions come out. Intimacy and reciprocity between doctor and patient were fundamental values that underlay the development of family medicine,[1] and almost every conversation between a patient and a doctor is best carried out in the environment of security and trust that comes with someone who knows us and accepts us for who we are.

One of my most vivid patient experiences was with a distinguished 70-year-old professor I had been taking care of for a decade, who suffered from a number of vexing somatic symptoms and whom, it seemed, I could never reassure enough. I got a call from the clinic one day saying that I needed to get there immediately; she was in a room and was hysterical and was willing to see only me. When I walked into the room, she sobbed that she could not keep it quiet any longer. I asked her what "it" was, and she told the long and painful experience of being sexually abused as a child and being too ashamed to ever talk about it with anyone. Why then, why me? Because I was her doctor and I was there when she needed me.

Medicine has come a long way toward opening up difficult conversations. Some of the earliest work on the prevalence of domestic violence in a general population and some of the barriers physicians found to asking about it was carried out in Wisconsin.[2] Wisconsin has led the way nationally in having end-of-life conversations,[3] even at the risk of being vilified as promoting death panels during the discussions that led to the enactment of the Affordable Care Act. Both of those issues are now codified as part of the basic training of all medical students in the United States and all doctors should be able to ask about them, but those conversations often still happen between generalists and their patients.

Research on career choice repeatedly points out that a relationship with patients is the central value that motivates students to choose careers as generalists and the one that keeps them there after they finish training. Those relationships are sources of enormous satisfaction but also of great challenges. Perhaps the newest one for many of us is the discussion of sex trafficking that often underlies the sexual abuse, drug use, and behavioral issues in adolescents and adults.

One of the oldest adages applied to ordering tests—and one often ignored—is that if one asks the question, one has to live with the answer. But the hardest questions are the ones we feel least likely to be comfortable with since we are not prepared to deal with the answers. My most frequent conversations with residents in family medicine over the past 40 years have always centered on why they were reluctant to ask patients about drug and alcohol use, domestic violence and sexual abuse, reasons for incarceration, dealing with anger, sexual behaviors, and all the other things that lie deep, often untouched, and threaten the health of our patients and, by inference, our communities. The rise of HIV helped make questions about sexual practices and intravenous drug use normal today. But that was not true in the early days of AIDS and was a source of discomfort and strife in the medical community.[4] Fortunately, we have gotten better.

However, the article by Rabbitt[5] on childhood sex trafficking in this issue of the *WMJ* raises an area of inquiry that presents some of those same challenges to physicians that the hard questions of the past did. Training clinicians to use their trusting relationships with patients to look more deeply into the story behind sexual abuse and risky behavior is more important than ever, not simply because the problem of sex trafficking is growing nationally and worldwide, but because Rabbitt points out a number of ways to help those clinicians deal with the answers. There is help, and there is hope for us and our patients.

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WMJ

Development and Distribution of Educational Materials for Carbapenem-Resistant Enterobacteriaceae Among Acute and Long-term Care Facilities

Jessica J.F. Kram, MPH; Gwen Borlaug, CIC, MPH; Nasia Safdar, MD, PhD; Ajay Sethi, PhD, MHS

ABSTRACT

Introduction: Carbapenem-resistant Enterobacteriaceae (CRE) are multidrug-resistant organisms emerging in the United States. The Wisconsin Division of Public Health implemented mandatory hospital-based CRE surveillance starting in December 2011 and assessed educational needs of health care personnel to guide education for statewide CRE prevention.

Methods: Pre- and post-intervention electronic surveys were distributed to infection control practitioners and local health departments to determine success of educational intervention. Pre-intervention telephone interviews were conducted with infection control practitioners who reported at least 1 case of CRE.

Results: The pre-intervention survey indicated that 20 (34%) responding infection control practitioners distributed educational materials to patients or staff and 13 (57%) responding local health departments had some CRE knowledge. A pre-intervention survey and interviews identified the need for educational materials such as fact sheets, brochures, and toolkits. Five months after materials were produced and distributed, 31 (63%) responding infection control practitioners had shared educational materials with patients or staff and 11 (100%) responding local health departments indicated some CRE knowledge.

Conclusion: Overall, use of CRE educational material increased and improved general CRE knowledge among health care personnel following development and distribution of educational materials. Small sample size prevents determination of statistical significance between pre- and post-intervention responses.

BACKGROUND

Enterobacteriaceae are a group of gram-negative commensal human gut bacteria that are important causes of urinary tract infections, pneumonia, and bloodstream infections.[1,2] Major species within the Enterobacteriaceae family include *Escherichia, Klebsiella,* and *Enterobacter.*[1]

In recent years, resistance to many classes of antibiotics has emerged among Enterobacteriaceae. The most alarming recent development is the emergence of carbapenem-resistant Enterobacteriaceae (CRE). CRE are defined as Enterobacteriaceae that are nonsusceptible to doripenem, meropenem, or imipenem and are resistant to third-generation cephalosporins.[2]

Throughout the late 1990s, new mechanisms of carbapenem resistance emerged, predominately among *Klebsiella pneumoniae* and *Escherichia coli*, typically conferring resistance to all the β-lactam agents except aztreonam.[3] These organisms produce metallo-beta lactamase enzymes such as *Klebsiella pneumoniae* carbapenemase (KPC), first reported in the United States in 1996, and New Delhi metallo-beta-lactamase (NDM-1), found predominantly in India and Pakistan.[3,4] These metallo-beta lactam enzymes use carbapenemases to hydrolyze the beta-lactam ring of the carbapenems, leaving no option for treatment of CRE infections with beta-lactam agents.[1,5] Whereas the AmpC beta-lactamase mechanism of resistance is chiefly chromosome-mediated, genes associated with KPC and NDM-1 production are plasmid-mediated and can be transmitted easily among species of the Enterobacteriaceae family.[4,5]

Invasive CRE infections are associated with mortality rates of 40% to 50%, prolonged length of hospital stay, and higher health care costs when compared to infections with non–drug-resistant Enterobacteriaceae.[1,2,4,6] Individuals most at risk of CRE acquisition include patients treated with indwelling medical devices or

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antibiotics, those with underlying medical conditions, patients admitted to intensive care units, and residents of long-term care facilities.[1,2] Currently, CRE are predominantly health care-associated pathogens, but the potential for community transmission exists.[5] Hence, infection control and prevention efforts are crucial for reducing the risk of CRE.

In response to laboratory reports of CRE in Wisconsin, the Wisconsin Division of Public Health (DPH) initiated mandatory hospital-based CRE surveillance in December 2011.[7] Subsequently the Wisconsin DPH began regional CRE prevention activities in the Southeastern public health region, an area identified with relatively high CRE prevalence. In 2012, CRE prevalence (number of laboratory-identified CRE events/number of admissions x 100,000) in the Southeastern public health region was 7.3, while the remainder of the state was 5.5. During the first 6 months of 2013, CRE prevalence in the Southeastern public health region was 9.1, while the remainder of the state was 2.5. Educational materials also were developed following a needs assessment to identify CRE knowledge gaps.

METHODS

Statewide hospital-based CRE surveillance was conducted using the National Healthcare Safety Network case definitions for laboratory-identified CRE events.[7] The National Healthcare Safety Network is a Centers for Disease Control and Prevention surveillance system used for nationwide tracking of health care-associated infections. A total of 138 reporting facilities—71 Wisconsin acute care hospitals, 59 critical access hospitals, 2 children's hospitals, and 6 long-term acute care hospitals—were required to report inpatient CRE laboratory events to the Wisconsin DPH. Infection control practitioners were given CRE surveillance training via a webcast and a follow-up teleconference call prior to the December 2011 surveillance start date. A timeline of CRE education events is provided in a Table. All activities were public health-related and determined to be Institutional Review Board (IRB) exempt.

Assessments of CRE educational needs among health care personnel and local health department staff were conducted from January 2013 through October 2013 to identify potential need for CRE educational tools.[8] In February 2013, the Wisconsin DPH e-mailed a 6-question electronic survey to infection control practitioners working at facilities that were required to report inpatient CRE laboratory events and a 4-question electronic survey to 90 local health departments. Infection control practitioners were asked to indicate their public health region, whether they had participated in collaborative groups to provide CRE infection prevention strategies across the health care continuum, whether they had educational materials on hand to provide to direct care staff and/or patients, whether they had conducted at least 1 CRE educational activity within their facilities, and to specify educational materials they desired for further education of staff and patients. Local health departments also were asked to indicate their public health region, whether they worked with collaborative groups, and to specify educational materials they desired for further education. Additionally, local health departments were asked to indicate what knowledge they had regarding CRE risk factors, reservoirs, modes of transmission, prevention, and surveillance. All participants were instructed to complete the survey online within 2 weeks of receiving the survey.

In March 2013, telephone interviews were scheduled with infection control practitioners who had reported at least 1 case of CRE within their facility and who reported they had no educational materials available for staff or patient education. Participants were asked to identify their public health region, educational need, and barriers to interfacility communication regarding CRE status of patients and residents. Survey and interview responses were recorded. Educational materials—CRE fact sheet, educational brochure for health care personnel, and educational brochure for patients—were created and distributed to infection control practitioners and local health departments during April 2013.

Because statewide CRE surveillance identified relatively high prevalence of CRE in the Southeastern public health region and a concentration of CRE cases in Milwaukee County, the Wisconsin DPH and the City of Milwaukee Health Department convened an expert panel to develop a CRE toolkit for acute care and long-term care hospitals and for skilled nursing facilities. The panel comprised infection control personnel, communicable disease coordinators, public health nurses, hospital epidemiologists, and professional students. The toolkits incorporated the health care personnel and patient educational materials prepared in response to the survey results.

During August 2013, the City of Milwaukee Health Department hosted a CRE educational conference for hospital and skilled nursing facility staff who worked within Milwaukee County. The educational materials—previously distributed during April 2013—and the CRE toolkit were presented at this conference. Educational materials can be found here: http://www.dhs.wisconsin.gov/communicable/ARO/CRE.htm. Prior to the conference, participants were given a printed survey that asked them to identify whether CRE educational materials were available in their facilities for staff and patient education. Following the conference, participants were given a printed survey that asked them to evaluate whether the educational materials and toolkit were useful, whether they were easy to comprehend, and whether they would be used for further education. Participants also were asked to recommend any changes to these materials. Responses to both surveys were entered into a Microsoft Excel spreadsheet.

One month after the conference, the Wisconsin DPH e-mailed an 8-question electronic survey to the same infection control practitioners and an 8-question electronic survey to the same

Table. Timeline of Events for Carbapenem-Resistant Enterobacteriaceae (CRE) Education

Event	Timeline
CRE surveillance training via webcast and follow-up teleconference call	Prior to December 2011
Initiation of mandatory hospital-based CRE surveillance	December 2011
Assessment of CRE educational need among infection control practitioners and local health departments via electronic survey	February 2013
Telephone interviews with infection control practitioners who experienced first known cases of CRE in Wisconsin	March 2013
Creation and distribution of educational materials to infection control practitioners and local health departments	April 2013
The Wisconsin Department of Public Health and the City of Milwaukee Health Department convened expert panel for development of CRE toolkit	February 2013 – August 2013
CRE educational conference • Evaluation of educational materials and toolkit • Corrections to educational materials and redistribution	August 2013
Assessment of CRE educational tools by infection control practitioners and local health departments via electronic survey	September 2013

local health departments. Participants were asked the same questions as the pre-intervention survey questions. Additionally, participants were asked to evaluate whether the educational materials were easy to understand and to make suggested changes to the materials. All participants were instructed to complete the survey online within 2 weeks of receiving the survey request. Responses were entered into a Microsoft Excel spreadsheet. Differences between CRE knowledge, CRE educational activities, and the availability of CRE educational tools were assessed.

RESULTS

Surveillance Data

During 2012–2013, 45 unique hospital inpatients were identified among 27 acute care facilities. Among the 45 unique hospital inpatients identified, 36 (80%) were reported from facilities in the Southeastern public health region and 25 (56%) were reported from facilities in Milwaukee County.

Pre-intervention Survey

Among 58 infection control practitioners who completed the survey, 17 (29%) reported having CRE educational materials available for staff and 15 (26%) reported having CRE educational materials available for patients within their facilities. Additionally, 20 (34%) reported that they had provided CRE educational materials to staff or patients. A total of 55 (95%) infection control practitioners indicated fact sheets and 47 (81%) indicated educational pamphlets as preferred CRE educational tools.

Among 23 local health departments that completed the survey, 13 (57%) reported having some knowledge regarding CRE. Among the 13 local health departments that reported having CRE knowledge, 9 (39%) reported knowledge about risk factors, 6 (26%) reported knowledge about reservoirs, 10 (43%) reported knowledge about modes of transmission, 10 (43%) reported knowledge about prevention measures, and 1 (6%) reported knowledge about surveillance. A total of 23 (100%) local health departments indicated fact sheets, 14 (61%) indicated educational pamphlets, and 15 (65%) indicated surveillance data as preferred CRE educational tools.

Interviews

Four infection control practitioners—those who provided care to the first known cases of CRE in Wisconsin—were interviewed, and all identified that limited educational materials were available for educating staff and patients about CRE prevention. Each also indicated that no CRE protocols existed within their facilities prior to reporting their first case of CRE.

Pre- and Post-conference Survey

Among 36 infection control practitioners completing the pre-conference survey, 23 (64%) reported they had educational materials available for staff and 19 (53%) had educational materials available for patients. Among 35 infection control practitioners completing the post-conference survey, 34 (97%) stated that the educational tools were useful and 33 (94%) stated that the tools were easy to comprehend. Additionally, 27 (77%) reported they would use the educational tools for further CRE education.

Post-intervention Survey

Among 49 infection control practitioners completing the post-intervention survey, 37 (76%) reported they had educational materials available for staff and 31(63%) had educational materials available for patients. Additionally, 31 (63%) reported they had provided educational materials for patients or staff. Among 18 infection control practitioners from the Southeastern public health region, 15 (83%) reported they had educational materials available for staff, 13 (72%) had educational materials available for patients, and 12 (67%) had provided educational materials for patients or staff. Among 31 infection control practitioners from the rest of Wisconsin, 22 (71%) reported they had educational materials available for staff, 18 (58%) had educational materials available for patients, and 22 (71%) had provided educational materials for patients or staff.

Among 11 local health departments completing the post-intervention survey, 11 (100%) reported some knowledge about CRE. Local health departments reported that they had increased knowledge regarding risk factors (91%, n=10), reservoirs (55%, n = 6), modes of transmission (82%, n = 9), prevention measures (91%, n = 10), and surveillance (45%, n = 5) as it relates to CRE.

Infection control practitioners and local health departments also were asked to evaluate the educational materials based on

their usefulness and comprehension. Overall, 37 (76%) of infection control practitioners responded that the educational materials were very useful or somewhat useful and 44 (90%) found them easy or somewhat easy to understand. Similarly, 8 (73%) local health departments responded that the educational materials were useful or somewhat useful and 9 (82%) found them easy or somewhat easy to understand.

DISCUSSION

Infections with CRE are a developing public health crisis in the United States and worldwide. Thus, a keen understanding of the epidemiology of CREs is critical to devising and implementing strategies for prevention. We found that in our study sample of infection control practitioners and local health departments—individuals at the frontlines of identifying and preventing CREs—self-reported knowledge regarding CRE and educational materials to facilitate understanding was largely lacking. This is an important area upon which to intervene because education of health care personnel and local health departments is a key component of CRE prevention. Although survey participation was low, we found that following the development of educational materials, most infection control practitioners reported that the materials were easy to understand, and they intended to use them in their practices. Furthermore, these materials and data collected serve as a useful starting point for further refinement in the future.

Increased availability and accessibility of CRE educational materials in the Southeastern region suggest that the intervention was well targeted among those with increased need. However, the fact that responses in the Southeastern public health region indicated increased availability and use of educational materials from those in the remaining regions may be a result of higher CRE prevalence or awareness. Practical experience with CRE cases also likely had a positive impact on CRE knowledge levels among infection control practitioners and local health departments in the Southeastern public health region.

Our study has implications for health care personnel in CRE prevention and represents an important step toward CRE prevention in Wisconsin. Incorporating pre-intervention phone interviews with front line staff directly involved in the care of patients with CRE is a strength of our study as we used those data—on type of materials available and types of materials desired—to develop our intervention. Educational materials are most likely to be used when developed in collaboration with endusers. Thus, we believe that our approach may provide a framework for other agencies and institutions developing educational materials on CRE.

Our study has a number of limitations. Determining the statistical significance of differences in pre- and post-intervention responses was not possible because of the study's small sample size. There is also the possibility of self-selection of respondents with higher CRE awareness. Additionally, the impact of the CRE educational tools on patients' knowledge of CRE was not determined, and the effect of CRE education on reducing CRE incidence was not determined. Nonetheless, a public health response to emerging health care threats must always include an educational component for health care personnel, patients, and families. Future studies should examine the impact of these strategies on CRE prevention.

CONCLUSION

Infection control practitioners reported increased access to and use of CRE educational materials following production and statewide distribution of health care personnel and patient pamphlets and fact sheets. CRE conference attendees indicated that the CRE educational materials were useful and comprehensible. Local health department staff also reported higher levels of knowledge regarding CRE following distribution of these materials.

Statewide CRE surveillance, education, and prevention continue through partnerships with the Wisconsin DPH and hospital and nursing home health care professionals. Targeted CRE prevention continues in Southeastern Wisconsin through an ongoing partnership with the City of Milwaukee Health Department. CRE collaborative activities have been expanded to other regions of the state through partnerships with the Wisconsin Chapters of the Association of Professionals in Infection Control and Epidemiology (APIC) and the Wisconsin Associations of Local Health Departments and Boards (WALHDAB).

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The Medical Response to Sex Trafficking of Minors in Wisconsin

Angela Rabbitt, DO, FAAP

ABSTRACT

Medical professionals are in a unique position to identify and assist pediatric victims of sex trafficking, who experience a high prevalence of physical, mental, and sexual health problems. However, providers report a need for education and guidelines for medical care of this population. A literature review was conducted on the nature and scope of pediatric sex trafficking in Wisconsin, the medical and mental health needs of victims, and existing guidelines for medical management. Few existing medical guidelines for the care of trafficking victims are specific to pediatrics or include specific recommendations for the forensic medical evaluation. Because of legislation and resources specific to Wisconsin, national guidelines may not apply locally. Based on the literature review, as well as input from community partners and medical professionals who frequently provide services to victims, guidelines for the medical care of pediatric sex trafficking victims in Wisconsin were developed. Additional community barriers that may prevent an effective medical response also are discussed.

INTRODUCTION

Recent improvements in community awareness of sex trafficking have sparked awareness of this issue among medical professionals. However, providers in Wisconsin report a poor understanding of sex trafficking, have little confidence in their ability to identify and assist trafficking victims, and often underestimate the scope of the problem locally. A lack of awareness and access to medical guidelines is reported as a barrier to identification and an effective response.[1]

Definition of Pediatric Sex Trafficking

Wisconsin state law defines sex trafficking of a child as knowingly recruiting, enticing, providing, obtaining, or harboring a child for the purpose of a commercial sex act, or sexually explicit performance.[2] A child is defined[3] as any person under the age of 18, and a commercial sex act is sexual contact for which anything of value is given to, promised, or received, directly or indirectly, by any person.[4] This broad definition also includes pornography, stripping, and other sexually explicit performance. Additionally, those who procure children for the purpose of selling sexual contact, as well as buyers of sexual contacts with children (including those who pay with food, shelter, and other survival needs) can be considered traffickers under Wisconsin statutes.[5] Children lack the maturity and experience to make informed choices about sex and are vulnerable to exploitation. For this reason, proof of force, fraud, or coercion is not required in the legal definition of sex trafficking for victims under 18 years of age.[5] Sex trafficking does not necessarily involve transportation of the child into the United States from another country, or even movement across state or county lines.[6] In fact, 83% of victims identified by the federal government between 2008 and 2010 were US citizens.[7] In Wisconsin, the majority of victims are recruited locally.[8]

Traffickers may be family members, acquaintances, or strangers to the victim. In Wisconsin, the most common forms of trafficking were parents or other caregivers selling children for money or drugs, and runaway minors trading sex for a place to stay or to meet basic needs.[9] Youth are particularly vulnerable to recruitment. Among adolescents victimized in the sex trade, the average age of entry was 12 to 15 years.[10-12] Traffickers preferentially prey on children and youth with low self-esteem and minimal social support.[13] Not surprisingly, many victims have a history of physical abuse, sexual abuse, or neglect.[8,14]

The Role of Medical Providers

In its 5-year strategic plan, the US Department of Justice reports the need for enhanced coordination between service providers to improve victim identification and referral to necessary services.[15] Individuals who enter the sex trade prior to the age of 18 frequently

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report severe physical and sexual violence.[16,17] They often experience inadequate diet and hygiene, substance abuse, neglect, pregnancy, and poor access to health care.[18] Psychological abuse associated with removal from their families, isolation, ongoing threats, and witnessing the abuse of others can cause profound and lasting effects on their health and well-being. As a result, this population experiences high rates of depression, post-traumatic stress disorder, anxiety, and somatic complaints.[19] Because of victims' complex medical and mental health needs, medical professionals are in a unique position to identify and assist them.

Once victims are identified, the role of health care professionals is to identify and treat unmet medical needs, assist with evidence collection for legal purposes when appropriate, and provide resources for ongoing physical and mental health needs. In addition, medical providers can help educate community providers about the unique medical and mental health needs of this population. In a 2013 assessment of human trafficking in Wisconsin, community providers (law enforcement, prosecutors, victim advocates, and social service providers) reported that only 5% of trafficking victims identified by their agencies were referred for health care.[20]

The Scope of the Problem in Wisconsin

Because victims are difficult to identify and no comprehensive centralized database of victims exists, the number of children involved in the sex trade is unknown.[6] According to the US Department of State, approximately 2 million children are being exploited globally.[21] In a recent representative sample of US adolescents, 3.5% disclosed they had exchanged sex for drugs or money in their lifetime.[22] Additional research is needed to explore the incidence and demographics of trafficked youth in Wisconsin. As of 2007, trafficking victims had been identified in over half of Wisconsin's 72 counties. These victims were from both urban and rural locations.[6] In the most comprehensive local study to date, 77 child victims were identified by law enforcement in Milwaukee County between 2010 and 2012. Approximately 20% of these victims were not from Milwaukee, but were trafficked into the city from more rural areas throughout Wisconsin.[8] The total number represents only those youth in contact with the Milwaukee Police Department. Given the problems in identifying these youth, it is likely a gross underestimate of the actual number of children affected by trafficking. Medical and mental health professionals at the Children's Hospital of Wisconsin and Milwaukee County Juvenile Detention Center began tracking victims in January 2014. This research is ongoing, but suggests that the number of victims is significantly higher than indicated in previous studies. (T. Medley, APNP, W. Ehrman, MD, written communication, January 2015).

Identification of Children at Risk

Victims have varied demographic characteristics. They come from broken and intact families, urban and rural areas, wealthy communities and high poverty areas. They may live at home, on the street, or alternate between the two.[20] Decisions to screen should not be based on any single characteristic. However, some populations (especially runaway youth, youth with a history of exposure to violence and abuse, lesbian, gay, bisexual, transgender, questioning [LGBTQ] youth) do possess vulnerabilities that place them at higher risk.[23] In Milwaukee County, the majority of victims identified by law enforcement were African American (78%) and female (92%), and 70% of victims had been reported missing at least once in their lifetime.[8] While most victims were female, trafficking of men and boys may be under-identified and is likely significantly higher than reported.[24] Boxes 1 and 2 are a summary of psychosocial risk factors and medical conditions that are common in victims of sex trafficking. Providers should consider screening for sex trafficking when children present with these risk factors and indicators.

Screening Potential Victims of Trafficking

Unfortunately, identification of victims is often difficult. Victims may not identify themselves to providers because of threats and coercion by their trafficker, self-blame, and the stigma of "prostitution." They may have a history of negative interactions with law enforcement or child protective services, or may believe that they are criminals and will be incarcerated or punished for prostitution. They may demonstrate self-protective behaviors such as hostility and distrust toward providers. Some victims lack insight about the true nature of their relationship with the trafficker and don't identify as victims. Despite the abuse victims often experience at the hands of their trafficker, victims who have experienced physical or sexual abuse at home may feel they are better cared for by the trafficker than by their family. Medical professionals should attempt to gather information needed to make medical and safety decisions, but realize that a full disclosure may not occur at the time of the initial interview.

Interactions with potential victims should be honest and nonjudgmental, with the goal of creating a safe environment for disclosure when the patient is ready to seek help. In order to facilitate trust, consider discussing the limits of confidentiality prior to taking the medical history or proceeding with screening questions. Whenever maltreatment is a concern in an adolescent patient, including trafficking, the history from the child should be taken separately from the caregiver. If a child who does not speak English presents with an English speaking caregiver, an independent translator should be called to assist in communication with the child. Ask open ended questions without the use of technical terms that the child will not understand such as "trafficking." Because they imply culpability on the part of the child, use of terms like "prostitution" also is discouraged.

There are currently no evidence-based screening tools for the identification of sex trafficking in minors.[24] The screening questions in Box 3 are modified from other published guidelines[25,26] and sug-

Box 1. Risk Factors and Indicators of Sex Trafficking in Minors[6,7,12,23,24,25,26]

- Recurrent AWOL (absent without leave/runaway) behaviors.
- Youth in shelters or group homes.
- Homeless youth.
- Youth from other areas (international or within the United States) who recently relocated or have been removed from a supportive social network.
- Pregnant adolescents, adolescents concerned about being pregnant or who have had multiple abortions.
- Adolescents with sexually transmitted infections or with concern for sexually transmitted infections.
- Adolescents with unexplained injuries.
- Patients brought for medical care by unrelated caretaker who may seem controlling or "talk for the patient."
- Adolescents who appear to have money, gifts, or clothing (especially sexual dress) with no prosocial source or that was provided by an older individual.
- Youth who report they "dance" for money.
- Youth familiar with language commonly used in the sex trade (examples include "bottom," "stable," "the game," "daddy").[25]
- Youth whose identification or cell phone has been taken from them.
- Prior history of sexual abuse or assault, neglect, or physical abuse; Child Protective Services involvement.
- Branding/tattoos.
- Youth with an anxious or fearful presentation, flat affect, or submissive demeanor; information appears to be recited.
- Youth with peers or family members involved in the sex trade.
- Youth who provide false or changing demographic information.

Box 2. Medical Conditions that May Affect Trafficked Youth[19,24,25]

- Reproductive health problems, including exposure to HIV and other sexually transmitted infections, fertility issues, and other gynecological diagnoses associated with sexual violence and rape.
- Pregnancy.
- Physical health problems associated with beatings and rapes—evidence of cigarette burns, untreated fractures, sexual abuse, bruises, lacerations, skin injuries may be hidden by clothing.
- Self-injurious behavior such as cutting.
- Blood-borne infections from tattoos or brandings.
- Untreated chronic medical conditions.
- Mental health issues—depression, post-traumatic stress disorder, anxiety disorders, oppositional behaviors, attachment disorder, aggression, attention deficit and hyperactivity disorder, and somatic complaints (headaches, chronic pain) associated with chronic stress and trauma.
- Malnutrition (may be thin or obese).
- Substance abuse—this may be forced by the trafficker or used as a coping mechanism to deal with trauma and abuse.

gestions by community partners who work closely with trafficked youth. Youth are screened routinely for high-risk situations through use of the HEADSS (home, education, activities/employment, drugs, suicidality, and sex) tool. Many of the questions about possible trafficking also can be incorporated into these standard screening questions.

Mandated Reporting and Confidentiality

Unlike cases of sex trafficking of adults, mandated reporters are required under Wisconsin law to report to child protective services and/or law enforcement if the provider has a reasonable suspicion that a child seen in the course of professional duties may be or will be a victim of sexual abuse, including sex trafficking.[27] Dual reporting to both child protective services and law enforcement is best practice in suspected trafficking situations, even when the potential perpetrator is not a parent or guardian. Victims are at high risk for other forms of maltreatment such as supervisory neglect, physical, and sexual abuse. Child protective services may be a resource to the child and family.

Providers should report to the law enforcement jurisdiction where the trafficking occurred, if this can be determined. If the location of the trafficking event is unclear, or if it occurred in multiple locations, report to law enforcement in the jurisdiction of the clinic or hospital. The report to child protective services should be to the county in which the child resides. Reproductive health information in adolescents is generally confidential and cannot be disclosed by providers without the child's consent. However, any form of sexual exploitation is considered an exception to adolescent confidentiality laws.[27] Health care providers are allowed to share protected health information with law enforcement and child protective services when reporting suspected abuse and when the information is pursuant and relevant to an active child maltreatment investigation.[28] Box 4 lists tips to guide communication with investigators in suspected child trafficking cases.

Under most circumstances, parents/guardians have a right to obtain medical information about their children. However, health care providers are allowed to withhold medical information under certain circumstances:[29] (1) when the minor has the legal right to consent to care (eg, reproductive health care services, diagnosis and treatment of sexually transmitted infections [STI], emancipated minor); (2) when the minor obtains judicial approval for medical care; (3) when the parent/guardian agrees to allow the minor to receive confidential medical care; and (4) if disclosure of information to a parent/guardian may endanger the minor.

Care of At-risk Youth Without Clear Concerns for Trafficking

Many youth are not prepared to disclose their victimization. The decision to report to law enforcement and child protective services when an at-risk child has not disclosed trafficking is based on case-specific details. Often, other history discovered during screening for

trafficking will mandate a report to investigators. Child abuse pediatricians and providers at child advocacy centers throughout Wisconsin specialize in the medical care of victims of physical abuse, sexual abuse, and neglect. Child advocacy centers are multidisciplinary programs with services that include forensic interviewing, victim advocacy and support, and often medical and mental health services. These providers can assist with reporting decisions in difficult cases.

Regardless of whether the case is reported, consider providing a list of local resources for runaway or trafficked youth. Inform the child that exploitation of youth is common and these resources are for friends or for the child should he/she ever need them. Some victims may fear retaliation from the trafficker if the resource list is found. Providers can verbally give patients the number for the National Human Trafficking Hotline: 1.888.373.7888, which will direct the youth to local resources, or provide contact information on a small, foldable piece of paper.

Box 3. Modified HEADSS (Home, Education [ie, School], Activities/Employment, Drugs, Suicidality, and Sex): Screening Questions for At-risk Youth

Home
Who do you live with? Who can you talk to about things? What are the people you live with like? Do you get along with your family? What would you change about them?
Can you come and go as you please? Have you ever been kicked out, run away, or not had a place to stay?
Education/Employment
What grade are you in? What are your grades like? Do you ever skip school? What do you want to do when you are done with school?
Do you have a job? How do you make your money?
Activities
Help me understand what a day in your life is like. What kinds of activities do you do throughout the day? What do you do on weekends?
Do you have a boyfriend/girlfriend? How old is this person? How did you meet?
Drugs
Do you smoke cigarettes, weed? Have you ever tried drugs? Do you drink alcohol? How much? How did you get it? Do you ever get sick, pass out or have a hangover? Do you ever use drugs or alcohol to escape from reality?
Did you ever do anything you didn't want to do when you were high, drunk, or passed out?
Suicide/Safety
Do you ever feel sad or lonely? Have you ever had thoughts of suicide?
Do you ever get in fights with friends or with your boyfriend/girlfriend? What is it like when you fight? Ask about violence or abuse history (physical abuse, bullying).
Sex/Sexual Exploitation
How many people have you had sex with in your life? When was the last time you had sex? Have you ever been pregnant or had an STD? Do you use protection?
Have you ever done sexual things even though you didn't want to?
Over the years, we've heard about more and more young people turning to the streets to make money for themselves or for other people. Sometimes they tell us they trade sex or sexual type activities for money, clothes, a place to stay, drugs, or survival. Do you know anyone like that?[26]
Has anyone ever asked you to do sexual things for money or suggested it would be a good way to make money or get the things you want?
Sometimes people feel like they don't have any other options but to trade sex for money or survival or someone else has made them do it. Has that ever happened to you?

Screening questions specific to trafficking are in bold. In order to develop rapport, HEADSS questions are ordered so more sensitive questions are asked last.

Medical Management for Suspected or Confirmed Victims

Trafficking victims often do not present for medical care until it is urgently necessary. The initial evaluation should assess for any acute medical needs and screen for medical conditions common in trafficked youth (Box 2). Follow-up often cannot be assured in this population and victims may not be compliant with medical treatment because of control by traffickers, frequent relocation, or other reasons. Consider hospital admission for potentially serious illnesses that require close follow-up. Assess for any immediate safety concerns. Protocols for security during potentially violent situations involving trafficking victims should be clarified in advance. In order to monitor for violence or threats to the patient, ensure the child is not left alone. If a social worker is available, place a social work consult to perform a psychosocial assessment, assist with referrals, and assess resource needs.

When trafficking is disclosed and after addressing urgent medical and safety needs, perform a forensic medical evaluation or refer the victim for a forensic evaluation. Medical treatment and forensic evidence collection should be performed only with the victim's consent/assent. If the patient refuses a medical evaluation, provide information about the time frame for forensic evidence collection and prophylactic treatment for STIs and pregnancy as described below in case he/she should desire this evaluation in the future. In some cases, a forensic medical evaluation should occur urgently to maximize the likelihood of recovering forensic evidence or documenting injuries that may heal quickly. See Box 5 for general guidelines for triage decisions and the Figure for a flow chart summarizing medical guidelines for at-risk youth. Child abuse pediatricians and child advocacy center staff also can provide additional assistance about locations and timing of referrals and follow-up.

The Forensic Medical Evaluation

The forensic medical evaluation includes a medical screening for physical and sexual assault, as well as unmet medical and mental health needs. It also may include collection of forensic evidence from the victim's body, documentation of injuries, and prophylaxis for STIs and pregnancy. Medical professionals also can address victim's concerns about reproductive health and educate youth about

Box 4. Tips for Medical Documentation and Communication with Investigators

Thoroughly document any disclosures by the child/adolescent using quotes when possible.

Clearly identify concerns for sex trafficking when reporting to law enforcement and child protective services. In many locations, early identification of trafficking concerns will trigger protocols within investigative agencies that can improve the initial response to victims.

Investigators need to clearly understand the medical information. Avoid medical jargon in documentation and oral communications.

Advocate for trauma-focused mental health therapy for trafficking victims as well as any other medical follow-up.

Document what steps were taken to ensure the child's safety and any resources provided.

Avoid making distinctions between youth who state they are "pimped" and those who state they are independent. Further investigation often reveals involvement of a trafficker.

Emphasize that the child is a victim in need of services, rather than a juvenile offender. Avoid the term "prostitute" to describe victims verbally and in documentation. The level of understanding about the dynamics of sex trafficking and the culpability of child/adolescent victims will vary among investigators, other providers, and the general community.

Box 5. Triage Decisions for the Sexual Assault Medical Exam

Situations Requiring an Urgent Sexual Assault Medical Evaluation

An Urgent Evaluation is Indicated in Any of the Following Circumstances. The Victim:

1. Has a history of acute sexual assault fulfilling criteria for an evidence collection kit or prophylaxis for pregnancy and sexually transmitted infections (generally less than 120 hours after the last sexual contact).
2. Complains of medically urgent symptoms (eg: symptoms of a possible sexually transmitted infection).
3. Has a possible genital injury or suspicious injuries that require documentation and may heal (eg: minor vaginal bleeding, complaints of anogenital pain, suspicious skin injuries).
   a. Genital injuries must be photo-documented by colposcopy or digital camera. This can be done in the Emergency Department by a trained provider, by a Sexual Assault Nurse Examiner, or at a Child Advocacy Center (CAC).
   b. Cutaneous injuries should be photographed at a CAC or by law enforcement.
4. There are prominent mental health or safety issues and the provider feels it is not safe to release the child without further evaluation or investigation.

The Urgent Evaluation Should Occur in the Emergency Department if the Victim Has Any of the Following:

1. Severe anogenital bleeding.
2. An injury that may require surgical intervention.
3. Other unrelated medical problems requiring emergent attention.

Situations Appropriate for a Non-Urgent (Scheduled) Sexual Assault Medical Evaluation at a Child Advocacy Center

1. The last episode of sexual assault is remote (>120 hours).
2. The victim is asymptomatic.
3. There are no urgent mental health or safety concerns.
4. Follow-up can be assured.

STIs, pregnancy prevention, and safety. The evaluation should be performed in an emergency department by a physician, physician assistant, or nurse trained to collect forensic evidence, by a sexual assault nurse examiner, or at a local child advocacy center.

In postmenarchal victims, a speculum exam with evidence collection from the cervix should be performed if the child can tolerate the procedure. In prepubertal children, a speculum exam is not appropriate due to the low yield of evidence from the cervix in young children and discomfort to the child. Evidence collection is appropriate in all cases with sexual contact reported to have occurred within 72 hours of the medical exam. In pubertal victims receiving a speculum exam, providers should strongly consider evidence collection up to 120 hours and may consider collection up to 2 weeks after reported sexual contact. Sperm has been reported in cervical specimens for up to 2 weeks after sexual contact in adolescents and adults.[30,31]

Guidelines for postexposure prophylaxis for STIs in sexual assault victims are outlined by the Centers for Disease Control and Prevention.[32] Due to transient living conditions and control by traffickers, follow-up for positive testing cannot be assured in this population. Therefore, it is generally advisable to provide postexposure prophylaxis for pregnancy and common infections (chlamydia, gonorrhea, and trichomoniasis) to all adolescent victims when they first present for medical care after a sexual assault.[23,25] Consider HIV postexposure prophylaxis as well if the assault occurred within 72 hours of the exam. The risks and benefits of medications should be discussed with the patient.

Testing for HIV, hepatitis B and C, syphilis, and pregnancy should be performed in this high-risk population, and pregnancy prophylaxis can be given up to 120 hours after sexual assault. In adolescents, testing for common STIs (gonorrhea, chlamydia, and trichomoniasis) should be performed if the victim is not given prophylaxis; however, a positive test can result from either a pre-existing infection unrelated to the assault, or to inoculum (semen) from the assault. If prophylaxis is given, testing for these common STIs at the initial evaluation is at the discretion of the provider, but may not be forensically valuable in the adolescent population when some prior sexual contact may have been consensual. However, consider that the abuser and other sexual partners may need treatment, and testing in this population may be valuable from a public health perspective. Urine and vaginal nucleic acid amplification testing (NAAT) has higher sensitivity than culture for the detection of gonorrhea and chlamydia and has FDA approval for use in adolescents and adults. However, if the positive NAAT has legal implications, it must be confirmed by culture or by a second NAAT using a different DNA sequence.[32,33]

The medical history in cases of identified sex trafficking should include screening questions to identify a history of drug facilitated sexual assault. If there are current symptoms of altered mental sta-

tus or amnesia associated with sexual assault, or there is a history of symptoms within 4 days of presentation, obtain a urine drug investigation screen and specific tests for gamma hydroxybutyrate, ketamine, and flunitrazepam. Alcohol is also commonly used in drug-facilitated sexual assault. Consider obtaining a blood alcohol level if the child presents with current or recent symptoms of intoxication. Drug screening should include legal confirmation of any positive results.

Victims who have been acutely sexually assaulted should routinely receive a follow-up medical evaluation, usually 2 weeks after the initial medical visit. During this visit, providers should consider repeat pregnancy testing, a reevaluation for STIs, and reassessment of suspected or confirmed genital injury if indicated. It is also an opportunity to assess for additional advocacy resource needs and to establish primary care. It is particularly important in this-high risk population to address the need for contraception and ongoing reproductive health care. Because they offer specialized services for children and adolescents, follow-up at a child advocacy center is preferred.

Community Barriers: Next Steps for Wisconsin

In addition to the reported need for guidelines in identification and medical response to victims, health care providers report concern that once victims are identified, community referrals will not result in adequate services for victims. Like medical providers, community service providers in Wisconsin also self-report a lack of awareness and understanding of sex trafficking.[34] In addition, there are currently very few organizations capable of providing an early assessment for resource needs, safe shelter, and ongoing case management for victims.[20] Some states mandate that child protective services fill this role. In Wisconsin, child protective services currently provides services for victims of abuse and neglect, but individual counties have discretion in investigating reports of abuse when the suspected perpetrator is not a caregiver.[35] As a result, suspected victims of sex trafficking reported to child protective services in some areas of Wisconsin may not receive services through this organization.

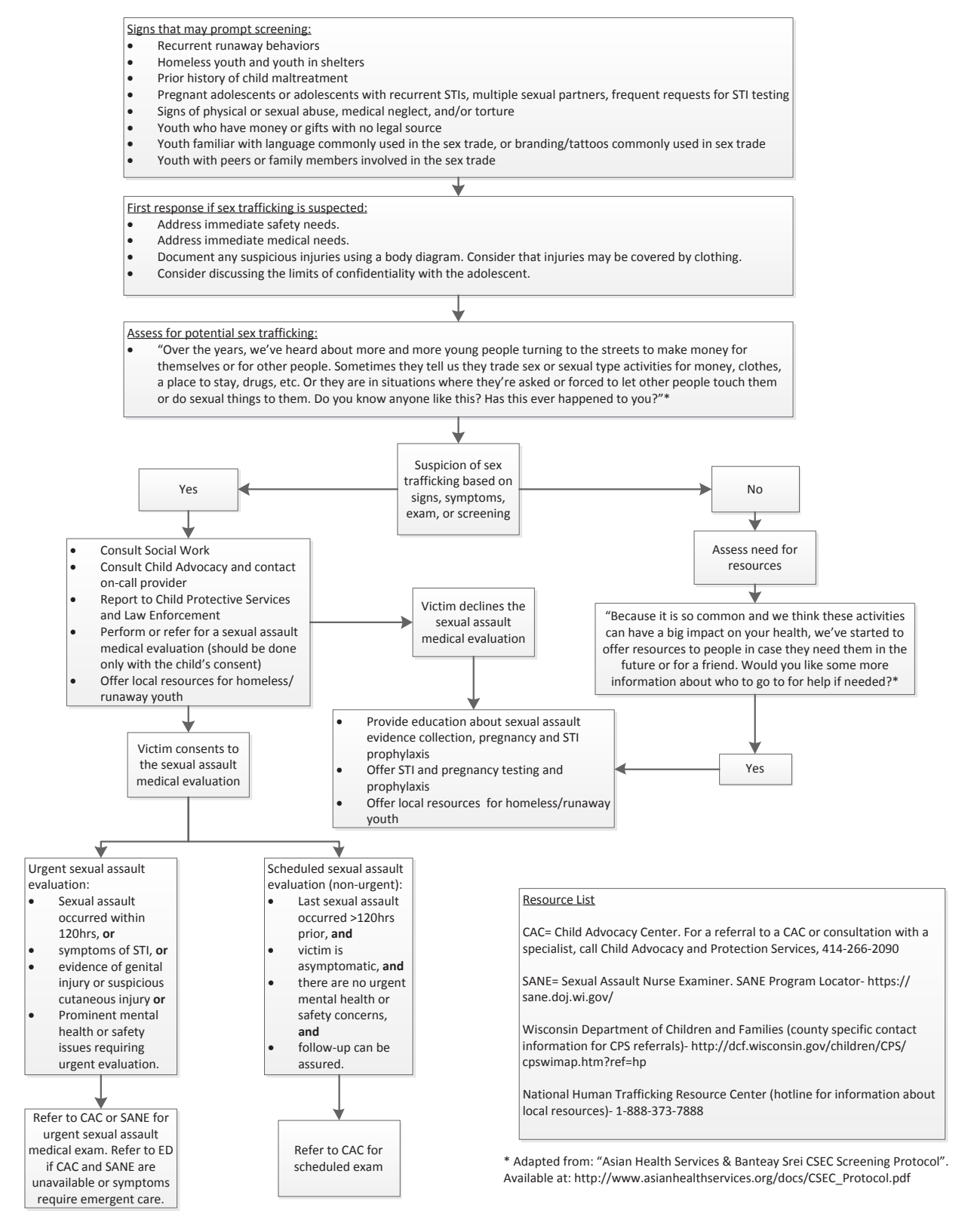
When cases are investigated, the child welfare system is generally set up to address the parents' behavior rather than to provide targeted services to victims of trafficking.[14,35] Victims of trafficking have unique medical, legal, and therapeutic needs which are different from the needs of child abuse victims.[36] Unlike the circumstances of child sexual abuse, where the wider community is usually supportive and sympathetic to victims, victims of trafficking more often receive inconsistent support as well as blame, and experience multiple levels of trauma throughout their victimization. Mental health resources that focus on the needs of child sexual abuse victims may not address the unique needs of trafficking victims. Residential facilities and group homes available to victims of physical and sexual abuse may not provide the security needed by trafficking victims, who are at risk for ongoing coercion and threats by traffickers. In addition to the psychological abuse and self-blame often imposed by traffickers, this lack of specific mental health and safety resources hinders the child's recognition of the situation and desire to seek help.[18] Unfortunately, the increased needs of this population present a challenge to community organizations with limited funding and staffing, including child protective services.[9,34]

Some victims may not disclose their exploitation for fear of prosecution, and some may be discouraged from seeking medical care because the medical evaluation may lead to proof of their involvement in the sex trade. Currently in Wisconsin, minor victims can be arrested and prosecuted for prostitution and other related charges. Prosecution increases distrust of law enforcement and other authority figures by victims and focuses too heavily on the culpability of the child rather than the exploitative nature of traffickers and buyers of sex.[14] Prosecution of minors for prostitution also contradicts statutory rape laws, which assert that minors are not legally capable of consenting to sex with an adult.[37] Some states prohibit prosecution of juvenile victims, or require courts to divert victims who are arrested for prostitution to specialized services (deferred prosecution).[38] New legislation in Wisconsin does limit the ability to prosecute minors and encourages deferred prosecutions.[39] However, with few options for secure shelter, juvenile detention centers may be the only option for victims during the early investigation and safety assessment.[14] Additional funds and efforts toward safe housing and effective victim-centered, trauma-informed services are needed.

Providers who work with at-risk youth in Wisconsin can attest to the widespread problem of trafficking, but those who do not regularly screen may not be aware of the scope of the problem. Additional research is needed to clarify the demographics and numbers of victims in Wisconsin, and how these victims access medical services. Such research could improve medical providers' willingness to screen and provide guidance on which specialties and locations are more likely to encounter victims. Validated screening tools that can be utilized in a busy office setting and evidence-based educational materials for providers that are convenient and easy to access also are needed. These resources could be used to develop county or hospital-specific guidelines and trainings in collaboration with local community partners.

Without the assurance of an effective response, providers may feel that identifying and reporting victims does more harm than good. However, every attempt to assist victims presents another opportunity for them to seek assistance. Identification of victims also provides opportunities to increase awareness and advocate for additional community services. Education of community partners and legislators by the medical community about the unique medical and mental health needs of pediatric sex trafficking victims in Wisconsin could help optimize services and minimize health

Figure. Decision Tool for Medical Management of Youth at Risk for Trafficking



Abbreviations: STI, sexually transmitted infection; ED, emergency department; CAC, child advocacy center; SANE, sexual assault nurse examiner.

disparities for this population. However, improved education and awareness within the medical community itself is an important first step.

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CME

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Quiz: The Medical Response to Sex Trafficking of Minors in Wisconsin

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Recognize the risk factors and indicators of sex trafficking in minors.
2. Describe the barriers of identifying at-risk youth victims of sex trafficking.
3. Identify potential screening tools to help mitigate these barriers.

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QUESTIONS

1. Which of the following statements about child sex trafficking is false?
   - ❑ Child sex trafficking is defined by Wisconsin state law as knowingly recruiting, enticing, providing, obtaining, or harboring a child for the purpose of a commercial sex act or sexually explicit performance.
   - ❑ For victims under the age of 18, proof of force, fraud, or coercion is not required in the legal definition of sex trafficking.
   - ❑ Sex trafficking by definition must involve transportation of a child into the United States from another country.
   - ❑ Traffickers may be family members, acquaintances, or strangers to the victim.

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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. You will receive an e-mail from wmj@wismed.org with instructions to complete an online evaluation. Your certificate will be delivered electronically.

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2. Which of the following is true regarding sex trafficking victims?
   - ❑ Most victims are female.
   - ❑ The average age of entry into the sex trade is 12 to 15 years old.
   - ❑ Many victims have a history of neglect, physical, or sexual abuse.
   - ❑ Higher risk populations include runaway youth, lesbian, gay, bisexual, transgender, questioning (LGBTQ), and youth with a history of violence.
   - ❑ All of the above.

3. Which of the following is true regarding the current challenges faced in Wisconsin in terms of addressing child sex trafficking?
   - ❑ Although higher risk populations can be identified, victims have varied demographics. For example, victims can come from both broken and intact families, urban and rural areas, and wealthy and poor communities.
   - ❑ Once identified, providers can refer victims to community organizations. However, community service providers report a lack of awareness and understanding of sex trafficking, and many organizations lack specialized support for sex trafficking victims.
   - ❑ There are currently no evidence-based screening tools for the identification of sex trafficking in minors.
   - ❑ No comprehensive centralized database of victims exists.
   - ❑ All of the above.

4. Currently in Wisconsin, minor victims can be arrested and prosecuted for prostitution and other related charges.
   - ❑ True
   - ❑ False

A Review of Clinical Signs Related to Ecchymosis

Narendranath Epperla, MD; Joseph J. Mazza, MD; Steven H. Yale, MD

ABSTRACT

Ecchymosis is a large area of discoloration caused by extravasation of blood into the subcutaneous tissue. It is an objective physical finding that may provide valuable clues as to its possible etiology. Ecchymosis is associated with eponyms based on the physician who first described the physical findings, which can be divided into 4 anatomical categories: base of the skull, abdominal wall and retroperitoneum, groin and scrotum, and lower extremity. Classic external signs and eponyms associated with ecchymosis are reviewed. Knowledge of these signs on physical examination may prove to be a useful clue directing the examiner to consider potentially serious causes of disease.

INTRODUCTION

Ecchymosis is defined as a large area of discoloration of the skin due to extravasation of blood into the subcutaneous tissue. The term is often used interchangeably with purpura, which describes similar characteristic discoloration of the subcutaneous tissue but usually is reserved for a larger, more extensive area of involvement. Ecchymosis is an objective physical finding that may provide valuable clues as to its possible etiology. The causes of ecchymosis are many; however, there are certain regions where the discoloration aids in the search for the etiology. The color of the subcutaneous tissue reflects the physiologic sequences of hemoglobin catabolism and its conversion to bilirubin and hemosiderin. Thus, the tissue progressively transforms over time from purple or black and blue to a yellow and green color and finally a brownish discoloration. It is recognized that the ecchymotic region will have different shades of color, reflecting differential rates of hemoglobin catabolism.

Ecchymosis caused by internal conditions can be divided into 4 anatomical areas (Table 1). These regions are assigned an eponym associated with the physician who first described the physical finding. In this report, we review the classical signs and eponyms associated with ecchymosis that may be markers of potentially serious internal bleeding. Furthermore, these signs may be potentiated by anticoagulation therapy or qualitative and quantitative platelet abnormalities. Prompt laboratory and imaging studies are important to further elucidate the cause of the ecchymosis and guide appropriate intervention. It is important that, in addition to a careful physical examination, a thorough review of the patient's medications and past medical history be conducted.

DISCUSSION

It was not until 1761, when Leopold Auenbrugger first described the technique of percussion, that the physical examination came into vogue. However, it did not become popular until 1808 when Jean-Nicolas Corvisart (personal physician of Napoleon) endorsed the importance of medical signs.[1] Shortly thereafter, Laennec invented the first stethoscope, expanding the horizon of physicians' senses.[2] The latter half of the 19th century saw steady improvement in new inventions including the ophthalmoscope (Hermann von Helmholtz, 1850), medical thermometer (Carl August Wunderlich, 1871), and sphygmomanometer (Riva-Rocci, 1896). Thus, physical signs gained importance and popularity by the beginning of the 20th century.[2,3] During this time period, there was a continued rise in new inventions and discoveries, as well as the emergence of novel diagnostic tests in medicine. Conducting a complete examination with cognizant focus on physical signs remained paramount for a physician to make a diagnosis. Several books and articles were published advocating the importance of the physical examination and providing

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Table 1. Classification of Ecchymotic Eponyms

Ecchymosis involving the anatomical regions	Eponyms
Skull	Battle sign
	Blepharohematoma or Raccoon eye sign
Abdominal wall and retroperitoneum	Grey Turner sign
	Cullen sign
	Stabler sign
Groin and scrotum	Fox sign
Lower extremity (thigh)	Meniscus sign

Table 2. Causes for Cullen Sign

Causes	References
Acute Pancreatitis	Bosmann et al[9]
Bilateral acute salpingitis in the presence of intrauterine pregnancy	Orient and Sapira[10]
Cirrhosis with portal hypertension	Orient and Sapira[10]
Hemorrhaging ascites from hepatic tumor	Mabin and Gelfand[11], Dalal and Mace[12]
Hepatocellular carcinoma	Orient and Sapira[10]
Hypothyroid myopathy	Orient and Sapira[10]
Ischemic and gangrenous bowel	Kelley[13]
Ovarian cyst hemorrhage	Orient and Sapira[10]
Percutaneous liver biopsy	Capron et al[14]
Perforated duodenal ulcer	Evans[15]
Retroperitoneal necrotizing fasciitis	Pryor et al[16]
Ruptured abdominal aortic aneurysm	Armour et al[17]
Renal sarcoma metastatic to the peritoneum	Orient and Sapira[10]
Rectus sheath hematoma	Guthrie and Stanley[18]
Splenic rupture	Chung et al[19]
Strangulation of ileum with hemorrhage	Orient and Sapira[10]
Strangulated umbilical hernia	Orient and Sapira[10]

Table 3. Causes for Grey Turner Sign

Causes	References
Acute Pancreatitis	Bosmann et al[9]
Bilateral acute salpingitis in the presence of intrauterine pregnancy	Orient and Sapira[10]
Ischemic and gangrenous bowel	Kelley[13]
Retroperitoneal necrotizing fasciitis	Pryor et al[16]
Ruptured abdominal aortic aneurysm	Armour et al[17]
Rectus sheath hematoma	Guthrie and Stanley[18]
Sclerosing peritonitis	Pryor et al[16]
Cardiac catheterization	Armour et al[17]
Intra-aortic balloon pump insertion	Rob and Williams[20]

education for physicians.[3] The latter half of the 20th century saw the advent of integrative medicine with continued technological advances in the field of medicine and the advent of sophisticated diagnostic aids. In the last decade or so, the major emphasis has been on diagnostic modalities with a declining focus on the physical examination. Educating physicians on history and physical examination skills required for optimal delivery of excellent clinical care is being reemphasized.[3] This review focuses specifically on physical signs related to ecchymosis, which are not only of historical interest but also are clinically important bedside observations for a possible etiology of the patient's condition.

Abdominal Wall and Retroperitoneum Ecchymosis

There have been a number of signs associated with ecchymosis of the abdomen or retroperitoneum named after the individual who first described the finding. These signs are markers for a potentially serious cause of internal bleeding and, according to the site of discoloration, are variously named as Grey Turner sign involving the flanks and Cullen sign involving the umbilicus.

Grey Turner Sign

In 1920, George Grey Turner (1877–1951) reported "dirty-green" discoloration appearing on the lateral abdominal wall in a patient with acute pancreatitis,[4] henceforth bearing his name to describe the condition. This sign is caused by extraperitoneal diffusion of blood from the posterior pararenal space to the lateral edge of the quadratus lumborum muscle, gaining access to the abdominal wall musculature through a defect in the transversalis fascia and eventually to the subcutaneous tissue of the flank.[5] The presence of this sign in patients with acute pancreatitis is associated with a mortality of nearly 40%.[6]

Cullen Sign

In 1918, Thomas Stephen Cullen (1868–1953), a Canadian-American gynecologist, first described a bluish discoloration of the periumbilical skin in a female patient with a ruptured extrauterine pregnancy.[7] Tracking of blood from the retroperitoneum to the umbilicus along the gastrohepatic and falciform ligament explains the pathophysiology of this sign.

Both Cullen and Grey Turner signs convey the same message, which is that intraperitoneal or retroperitoneal hemorrhage dissects to the subcutaneous tissue overlying the flanks or to the anterior abdominal wall, causing skin discoloration. However, the topographic location of the ecchymosis does not point to the etiology. Various theories have been proposed to explain the chemical properties required to develop these signs, including a direct role of pancreatic enzymes on the soft tissues and abdominal wall. On average, it takes 3 days for the appearance of Grey Turner's or Cullen's sign after the onset of pancreatitis.[6] These signs may be found in 1% to 3% of all cases of acute pancreatitis[5,6,8] and can occur in a broad range of clinical conditions (Tables 2 and 3).

Seat Belt Sign

The seat belt syndrome described by Garrett and Braunstein in 1962 refers to a pattern of sustained injury, including those involving the lumbar spine and visceral and solid organ injury, caused by the use of lap restraints.[21-24] Doersch and Dozier[25] first described the term "seat belt sign" in 1968 as linear ecchymosis of the abdominal or chest wall following a motor vehicle accident. The location of the ecchymosis (seat belt mark) on the subcutaneous tissue overlays the position of the lap or diagonal strap on

the seat belt at the time of the accident. The contusion sustained at the time of the impact is believed to be caused by mechanistic forces directed to the abdomen or chest at the time of deceleration or impact. Patients with this sign who sustain more serious intra-abdominal injuries are more likely to be in the passenger seat position when other independent confounding factors such as crash severity and impact have been accounted.[26]

Chandler et al[27] reported the presence of an abdominal seat belt sign in 14 of 117 cases. Of these 14 cases, two-thirds had an abdominal injury. Wotherspoon et al[28] performed a 6-year retrospective chart analysis of patients with abdominal wall and intra-abdominal injuries and reported no difference in intra-abdominal injuries between those people with or without a seat belt restraint. Velmahos et al[24] prospectively reported a 4-fold and 8-fold increase in thoracic and abdominal trauma respectively in patients with the seat belt sign compared to those without this finding. Thus, the sign lacks sufficient sensitivity and specificity in itself, and the presence of other physical findings in the appropriate setting may warrant serial clinical assessments and additional diagnostic evaluation or surgical exploration.[29]

This same principle applies to the presence of this sign in area of the neck.[30] In children, Paris et al[31] identified that the presence of free intraperitoneal air, lumbar fracture, and pulse rate higher than 120 beats per minute in the presence of seat belt sign was predictive of intra-abdominal injury warranting abdominal exploration. Furthermore, the absence of abdominal pain or tenderness in the presence of seat belt sign may be associated with a lower rate of serious intra-abdominal injuries.[32] Other factors that increase the likelihood of intra-abdominal injury include rebound tenderness, abdominal distention, guarding, and hypotension.[32] The presence of a seat belt sign is associated with an increased likelihood of musculoskeletal (eg, rib fracture), solid (eg, splenic, hepatic, and pancreatic), and hollow viscera (eg, mesenteric and intestinal) injuries.[33,34] Conversely, its absence does not exclude underlying visceral injury. There is currently no model that incorporates a variety of clinical factors to determine which patient does or does not require further diagnostic evaluation to exclude intra-abdominal injury.[20,35] Thus, an approach that includes a search for and recognition of this sign is of particular importance in patients with altered mental status or who are unable to cooperate with the examination due to other injuries.

Groin and Scrotum

The Blue Scrotum Sign of Bryant

The blue scrotum sign of Bryant as described in 1903 refers specifically to ecchymosis caused by a ruptured abdominal aortic aneurysm (AAA) extending into the scrotum.[36] Identification of this area of ecchymosis due to ruptured AAA is rare and may involve a region from the anterior abdominal wall, perineum, scrotum, lumbar regions, and in some cases extending to the knee.[37] In some cases, the ecchymosis may resemble Cullen and Grey Turner signs. The ecchymosis may be continuous or patchy, bilateral or unilateral, and may involve the lower extremities.[38] This sign is typically first seen 3 or 4 days after the initial symptoms of pain, but may present hours[39] or even weeks after rupture.[40]

In Bryant sign, blood must transverse the inguinal canal and spermatic cord down to the subcutaneous scrotal tissue. For Bryant sign to occur, there needs to be a coexistence of certain peculiar and specific clinical circumstances including a closed (retroperitoneal hematoma) or sealed (surrounding retroperitoneal and aortic tissue) rupture. In addition to the mode of rupture, the rate of leakage and a prolonged interval prior to final rupture also bear importance. Ecchymosis typically appears within 3 to 6 days after rupture of AAA.[38,39-41] The delay is accounted for by the time it takes blood to extravasate the facial planes to reach its final destination, which is presumably influenced by the volume of blood loss and patient's dependent position.

Stabler Sign

In some cases of retroperitoneal hemorrhage, the blood may extravasate and cause discoloration of the inguinal-pubic area.[42] This sign originally was described in adult patients suffering from acute hemorrhagic pancreatitis or ruptured ectopic pregnancy. Subsequently, it has been reported in various other conditions including AAA rupture. Although rare, this sign is most commonly identified in neonates secondary to adrenal hemorrhage.[43,44] Obstetric injury, perinatal hypoxia, and sepsis are common causes for neonatal adrenal hemorrhage. A nonsurgical approach is generally recommended when ecchymotic sign is present in a neonate;[43] however, rarely, it may be due to ruptured neuroblastoma, in which case prompt search for underlying adrenal malignancy should be undertaken.[45]

Thigh

Fox Sign

JA Fox, in 1966, reported 2 cases where bruising was noted in the upper outer aspect of the thigh caused by acute suppurative pancreatitis in one, and a ruptured AAA in the other.[46] In both cases, this sign was noticed late in the course and is produced by tracking of the fluid extraperitoneally along the fascia of psoas and iliacus beneath the inguinal ligament until it becomes subcutaneous in the upper thigh.[46] This sign has been described in other settings including strangulated ileum, urethral instrumentation, reaction to subcutaneous injections, and pulmonary infarction.[13]

Skull

During the evaluation of an injured patient, it is important to search for and expeditiously diagnose a skull base fracture (SBF) due to its high morbidity and mortality. This can be done by computed tomography (CT) imaging of the head.[47,48] Diagnosis may be delayed, since the patient's general condition may prevent prompt imaging. In this situation, the physician needs to rely on clinical signs and symptoms. Described are raccoon eye

sign (RES) and Battle sign, 2 important clinical signs associated with fractures of the base of the skull. Both of these signs are associated with a high positive predictive value for the presence of skull fractures and intracranial lesions.[49] In a postmortem study by Herbella et al,[50] both signs were present in 24 of 50 cadavers (48%).

Blepharohematoma or Raccoon Eye Sign

Trauma to the frontal region of the skull may cause a fracture to the anterior cranial fossa and rupture of venous structure at its base, leading to bleeding that extravasates to the regions of the eyelid and orbital adipose tissue. This sign has a high positive predictive value (PPV) for basilar skull fractures as well as for intracranial lesions.[49] Kral et al[48] identified RES in 14 of 67 patients (21%) with frontal fractures, while Goh et al[47] reported RES in 52% of patients with skull base fractures, of which 28% had concomitant clinical signs. Thus, RES is a useful clinical feature suggestive of basilar skull fracture.[47,48,50,51]

Battle Sign

Mastoid ecchymosis or retroauricular ecchymosis, also known as Battle sign, is a clinical indicator of base of the skull fracture in the posterior cranial fossa. This sign is named after Dr. William Henry Battle (1855-1936), an English surgeon.[52] The presence of this sign is associated with a high positive predictive value (>75%) for the presence of an associated basilar skull fracture,[49,53] so its presence should raise high suspicion and further diagnostic imaging for the presence of a basilar skull fracture.[54] A recent report described a case of hepatic encephalopathy with blepharohematoma and mastoid ecchymosis in the absence of trauma.[55]

Disruption of the emissary veins that travel from the sigmoid sinus to the postauricular soft tissue result in the retroauricular ecchymosis. This sign is caused by blunt trauma to the mastoid or temporal bone resulting in a longitudinal or mixed fracture within the temporal bone. Other associated findings that may be seen in longitudinal fractures include laceration of the external auditory canal, hemotympanum, facial nerve injury, and transient vertigo.[56] Battle[52] recorded that mastoid ecchymosis was often first observed 1 to 2 days after the injury, not immediately after the injury. When present, however, the patient is more likely to have a slower than expected recovery from head injury.

Knee

Crescent Sign

Good and Pozderac[57] reported 4 patients with gross blood in the knee and an acute synovial rupture syndrome. Each demonstrated ecchymosis that eventually reached the ankle, forming a crescent above 1 or both malleoli. The crescent sign is the presence of ecchymosis above 1 or more malleoli caused by synovial rupture in the presence of knee hemarthrosis. Hemarthrosis can result from trauma to the knee or from anticoagulant therapy or a bleeding disorder and is usually accompanied by painful swelling of the joint.[57] Spontaneous synovial rupture causes extravasation of blood through the fascial planes to the calf, extending to the ankle. This typically results in the disappearance and resolution of the knee effusion followed by pain and swelling in the calf. Therefore, in a patient who presents with pain and swelling of the calf, both synovial rupture and deep vein thrombosis should be considered in the differential diagnoses, with presence of a crescent sign suggesting the former.[57]

CONCLUSION

In 1890, Battle[52] described mastoid ecchymosis in 17 patients who had head injuries with fracture to the posterior aspect of the skull base. Bryant[35] described scrotal ecchymosis as a manifestation of ruptured AAA in 1903. In 1918, Cullen[47] first described a bluish discoloration of the periumbilical skin in a female patient with a ruptured extrauterine pregnancy, and in 1920, Turner[4] reported "dirty-green" discoloration appearing on the lateral abdominal wall in a patient with acute pancreatitis. In 1934 Stabler[42] described cutaneous discoloration of the inguino-pubic region in ruptured ectopic gestation, and Fox[46] described bruising in the upper thigh in 2 cases (acute pancreatitis and ruptured AAA) in 1966. These cases describing the ecchymotic signs occurred at a time when there were no sophisticated diagnostic aids, but it was the careful clinical acumen of the astute clinicians that helped unravel the pathophysiology related to these ecchymotic signs.

In addition to diagnoses associated with these classical signs or eponyms, consideration must be given to anticoagulation therapy as well as qualitative and quantitative abnormalities of platelets that may precipitate or exacerbate bleeding. It is vitally important that in addition to a careful physical examination, a careful history of the patient's medications and past medical history be obtained to help determine the etiology of these clinical signs.

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Tolvaptan for SIADH in Myelodysplastic Syndrome with Blast Crisis

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ABSTRACT

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of hyponatremia in cancer patients. It is most frequently reported in association with small-cell lung cancer, but has been reported in other cancers as well. Here we report the case of a patient with myelodysplastic syndrome and blast crisis who developed concurrent hyponatremia. The patient failed to respond to fluid restriction and administration of hypertonic saline. She was treated with tolvaptan, a vasopressin antagonist licensed for the treatment of adult patients with hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion. We conclude that in myelodysplastic syndrome patients with blast crisis, inappropriate antidiuretic hormone secretion should be considered as a cause of hyponatremia and be treated with tolvaptan.

INTRODUCTION

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) causes dilutional hyponatremia by increasing secretion of antidiuretic hormone (ADH) and water reabsorption in collecting ducts and is a common cause of hyponatremia in cancer patients.[1] SIADH has been reported most commonly in small-cell lung cancer, but has been described in other cancers as well.[1] In the literature, there is only 1 case report of SIADH in a patient with acute myeloid leukemia (AML) with multilineage dysplasia who developed hyponatremia and showed symptoms of SIADH through a mechanism similar to tumor lysis.[2] We report a case of hyponatremia from SIADH in a patient with myelodysplasia with blast transformation who showed a positive response to tolvaptan, a vasopressin antagonist licensed for the treatment of adult patients with hyponatremia secondary to SIADH.[3]

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CASE PRESENTATION

A 66-year-old woman was admitted to the hospital with chest pain. She had a diagnosis of myelodysplastic syndrome (MDS) and her most recent bone marrow aspirate showed hypercellular marrow with severe reticulin fibrosis and an increase in myeloblasts, suggestive of evolving MDS classified as refractory anemia with excess blasts-2 (RAEB-2). She received 4 cycles of azacitidine as an outpatient in anticipation of getting bone marrow aspiration before the fifth cycle. One week before hospital admission, her sodium level was 135-137 mmol/L (normal 133-144 mmol/L).

The patient was admitted for chest pain described as substernal, pressure-like, and nonpositional. Her physical examination was unremarkable, and her laboratory results showed a white blood cell count (WBC) of 13,700/μL (normal 4,100–10,900/μL) with 6% blast cells, 46% neutrophils, 26% lymphocytes, 11% monocytes, 1% basophils, and 10% myelocytes and metamyelocytes. Additional laboratory results showed normal hemoglobin (11.6 g/dL), platelets (213,000/ml), and creatinine (0.5 mg/dL) with low levels of sodium (133 mmol/L, normal 133-144 mmol/L) and urea nitrogen (5 mg/dL, normal 6–24 mg/dL), and an elevated D-dimer of 2.5 μg/mL (normal 0.1–0.67 μg/mL). A subsequent computed tomography (CT) scan of the chest was negative for pulmonary embolism, but the patient's bones were diffusely sclerotic due to underlying MDS, and this was determined to be the cause of her chest pain. She was started on narcotic analgesics for pain and continued on her home medications, including fluoxetine.

The next day, the patient's sodium level had dropped to 127 mmol/L, reaching 120 mmol/L in the next 2 days. Although the patient was euvolemic on clinical examination, her laboratory results showed low serum osmolality at 253 mOsm/kg (normal 282-305 mOsm/kg), urine sodium at 45 mmol/L, serum uric acid at 1.8 mg/dL (normal 2.3-6.4 mg/dL), and urine osmolal-

ity at 566 mOsm/kd (normal 500-800 mOsm/kg). Urinalysis revealed a specific gravity of 1.023 (normal 1.002-1.030) and was negative for protein and ketones. She had normal renal function and no evidence of hypothyroidism or adrenal insufficiency, but serum ADH, which was measured to confirm the SIADH diagnosis, was elevated at 3.5 pg/mL. These findings are consistent with the mild volume expansion expected in SIADH.

Table. Change in Serum Sodium Level, Urine Osmolality, and Urine Sodium Over Time

Day	Serum Sodium (mmol/L)	Intervention	Urine Osmolality (mOsm/kg)	Urine Sodium (mmol/L)
-7	137			
0	133	Admission		
2	127			
3	125		566	< 5
4	120		253	
5	117	Intensive Care Unit and 3% saline		
6	122	Fluoxetine discontinued, fluid restriction		
7	122	Fluid restriction		
8	122	Fluid restriction, tolvaptan (15 mg)	691	
9	124	Fluid restriction, tolvaptan (15 mg)	425	
10	129	Fluid restriction, tolvaptan (15 mg)		
11	133			45
25	133			

On the fourth day after admission, the patient's total WBC increased to 23,500/μL with 38% blasts. Approximately 40% of cells were circulating myeloblasts indicating evolution to (AML). Circulating myeloblasts were found to express CD45, CD34, CD117, CD33, CD13, HLA-DR, CD11b, and CD11c with CD64 expression at moderate intensity and no CD14 expression, suggesting no evidence of monocytic differentiation. This immunophenotype was quite different from the myeloblasts in the bone marrow, which were CD117-positive and CD34-negative.

By day 5, the patient's sodium continued to drop to 117 mmol/L, and she developed signs of altered mental status with confusion. She was placed in the intensive care unit overnight and started on a 3% saline infusion. With the diagnosis of SIADH as the cause of hyponatremia, fluoxetine was discontinued, and she was placed on fluid restriction. Subsequently, her sodium level increased to 122 mmol/L, and her mental status improved. She was continued on fluid restriction, and her sodium level remained at 122 mmol/L for the next 3 days. Urinalysis on fluid restriction showed an increase in specific gravity from 1.023 to 1.036, and urine osmolality increased from 566 to 691 mOsm/kg. On day 7, she was started on hydroxyurea 500 mg 3 times daily when her WBC increased to 38,000/μL. She also received packed red cell transfusions for worsening anemia and had worsening thrombocytopenia for which she did not require platelet transfusions.

On day 8, the patient's sodium level was 122 mmol/L, and she was started on tolvaptan 15 mg per day, which was continued for the next 3 days. Her sodium level increased progressively to 133 mmol/L (Table). Urine output on tolvaptan was 1 liter on day 1, 500 ml on day 2, and 1100 ml on day 3. She was in negative balance all 3 days.

Retrospectively, the bone marrow biopsy was sent for immunohistochemical analysis, and blast cells were negative for ADH.

DISCUSSION

Hyponatremia from SIADH is a common electrolyte abnormality seen in patients most often due to a small cell carcinoma of the lung and is rarely seen with other lung tumors.[4] Less common causes of malignancy-associated SIADH include head and neck cancers, olfactory neuroblastoma (esthesioneuroblastoma), and extrapulmonary small cell carcinomas. In the literature, there is one other case report of SIADH in a patient with AML with multilineage dysplasia who developed hyponatremia and showed symptoms of SIADH through a mechanism similar to tumor lysis.[2] This is the first case of hyponatremia from SIADH in a patient with myelodysplasia with blast transformation.

Evidence suggests that hyponatremia in cancer patients may be a negative prognostic factor,[1] making recognition and appropriate treatment particularly important. In the patient described here, the diagnosis of SIADH was based on clinical status and laboratory values after ruling out thyroid and adrenal insufficiency. It is also important to exclude the potential influence of drugs on hyponatremia. In the patient presented here, we began treatment of hyponatremia by discontinuing fluoxetine with fluid restriction. Fluoxetine has relatively slow elimination with a half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration.[5] The patient had been on fluoxetine for several months before admission with no history of hyponatremia. Sudden development of hyponatremia concurrent with development of AML prompted us to look for other causes, including blast-induced hyponatremia.

In patients with cancer, hyponatremia is often the result of SIADH and is thought to be caused by the ectopic production of arginine vasopressin (AVP) by tumor tissues or the effects of anticancer and palliative medications on AVP production or action.[6] In a single case report in the literature, blast cells were reported to stain positive for ADH in a patient with AML and SIADH.[2] In the present case, bone marrow was negative for ADH by immunohistochemical staining, but the interpretation and pathology results may be of limited value due to decalcification of the sample. Therefore, we are unable to rule out the tumor tissue as a source of ADH.

In the treatment of hyponatremia, hypertonic saline is indi-

cated for acute, symptomatic cases,[7] whereas fluid restriction is recommended to achieve a slower rate of correction for chronic asymptomatic hyponatremia. However, such measures may be insufficient to correct electrolyte imbalance in some. As illustrated in the case presented here, pharmacological therapy with tolvaptan may be necessary when fluid restriction is insufficient. Tolvaptan blocks the effects of AVP in the renal collecting duct to promote aquaresis, leading to a controlled increase in serum sodium levels by inducing free water excretion without increasing sodium excretion.[8] The effects of tolvaptan therapy in our patient were evident as serum sodium levels increased and urine osmolality decreased. Tolvaptan administration achieved a controlled increase in sodium levels to within the normal range, which fluid restriction failed to do.

Tolvaptan is available as 15 mg or 30 mg tablets. Treatment should be initiated at a dose of 15 mg once daily and titrated to a maximum dose of 60 mg once daily. Treatment is needed until the underlying cause of hyponatremia is corrected. Regular monitoring of serum sodium concentrations and volume status are necessary if tolvaptan is used in the outpatient setting. Tolvaptan therapy should be undertaken with caution due to the risk for adverse effects and potential drug interactions. Adverse effects reported most frequently include thirst and dry mouth, in addition to rarer reports of hypernatremia, pollakiuria, and polyuria.[9] Tolvaptan is metabolized by the cytochrome P450 isoenzyme CYP3A4, which is involved in the metabolism of a large number of common drugs, resulting in a high risk of pharmacokinetic interactions.[10]

CONCLUSION

The etiology of hyponatremia is diverse, and systemic evaluation is important for defining the cause and formulating a treatment plan. SIADH should be considered as a potential cause of hyponatremia in MDS patients with blast crisis. The vasopressin antagonist tolvaptan can be used to correct the hyponatremia if conservative treatments fail.

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Acute Central Vision Loss in an IV Drug User

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ABSTRACT

This report describes the case of a 21-year-old heroin user who presented with a 6-day history of decreased vision in her right eye, preceded by 1 week of headache and tender scalp nodules, neck stiffness, and photophobia. A broad infectious workup for acute vision loss was completed, and she was ultimately presumed to have acquired toxoplasmic chorioretinitis (ocular toxoplasmosis). We review the initial workup for chorioretinitis, and the epidemiology, diagnosis, and treatment of ocular toxoplasmosis. Intravenous drug users may be at increased risk of acquired ocular toxoplasmosis.

CASE PRESENTATION

A 21-year-old heroin user complained of 6 days of decreased vision in her right eye. Vision loss was preceded by 1 week of headache and tender scalp nodules, neck stiffness, and photophobia. On further review of systems, she had intermittent fevers and chills for the past 6 months that she attributed to withdrawal from heroin. Of note, she was actively still using heroin on a daily basis, with occasional marijuana and benzodiazepine use. She shared needles with her partner, with whom she was sexually active. She endorsed condom use for contraception.

Ophthalmic examination demonstrated counting fingers vision in the right eye and 20/20 vision in the left eye at near, normal intraocular pressures, and no evidence of inflammation in the anterior chambers. Dilated fundus examination demonstrated a 2 mm white chorioretinal lesion in the right eye involving the fovea with overlying vitritis. No lesion was seen initially in the left eye. The optic nerve was healthy as was the visualized periphery. There was no adjacent chorioretinal scar identified. She was admitted late in the evening on day 1, and her presenting exam was significant for nuchal rigidity, a positive Brudzinski's sign, numerous tender nodules on her scalp, and track marks on her upper extremities. She was afebrile and her vital signs were appropriate.

A urine pregnancy test was negative. Her white blood cell count was 10.1 with an absolute lymphocyte count of 3131. A lumbar puncture was attempted overnight but unsuccessful. Blood bacterial and fungal cultures were drawn, as well as a variety of fungal and parasite antibody tests including *Toxoplasma* serum IgM and IgG, *Histoplasma* serum antibody and urine antigen, and *Blastomycoses* urine antigen. She was treated empirically with voriconazole, vancomycin, and ceftriaxone. Ampicillin was also started due to concern for Listeria as we did not initially know the patient's HIV status. Rapid HIV testing was negative the following morning and HIV RNA was not detected. She was not checked for any other form of immunocompromise as she had no history of transplant or chronic steroid use and her initial blood counts were not indicative of a cell-mediated defect. Hepatitis labs were drawn because of her intravenous drug use, which showed immunity to hepatitis B and absence of hepatitis C RNA. She did have a successful lumbar puncture in interventional radiology on the morning of day 2. Cerebrospinal fluid (CSF) was clear and colorless and Gram stain revealed no organisms. Cell count and chemistries were atypical for meningitis. CSF culture was negative.

Although vitreous sampling would have been helpful diagnostically, it was not done because ophthalmic examination was stable with systemic therapy alone (Figure: A, B). Infectious disease was consulted, and ampicillin and ceftriaxone were switched to cefepime on day 3. A transthoracic echocardiogram for a possible septic embolic source was negative for vegetations. Magnetic Resonance Imaging (MRI) of the brain was also nega-

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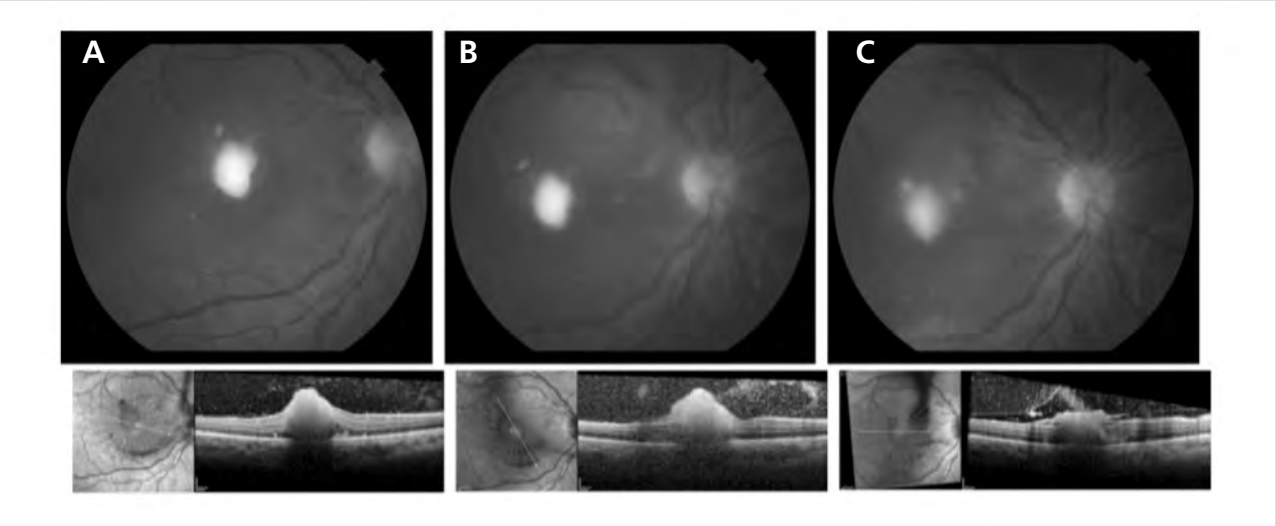
Figure. Progression of Patient's Ophthalmologic Exam



Fundoscopy and optical coherence tomography (OCT) images show patient's ophthalmologic exam on (a) day of admission; (b) 4 days after admission; (c) 2 weeks after admission.

tive. On day 4, *Toxoplasma* IgM returned positive (1.70 IU/ml, range 0.0-0.99 IU/ml), and IgG returned negative (< 0.2 IU/ml). Because of the association of acquired *Toxoplasma gondii* infection with cat exposure, further history was obtained from the patient, which did not reveal any significant feline exposure. She began treatment for acute toxoplasmic chorioretinitis with pyrimethamine, leucovorin, and sulfadiazine. Empiric antibacterials and antifungals were stopped on discharge (day 6), as her bacterial and fungal blood cultures were negative. Sulfadiazine was changed to clindamycin on discharge due to cost of medication. She was also prescribed a prednisone taper until follow up with ophthalmology.

On discharge, her scalp nodules had decreased in size and were no longer tender. They were thought to be lymphadenitis secondary to acute *Toxoplasma* infection. While we did not biopsy these lesions during her admission, this may have been a useful non-invasive way of ruling out a concomitant infection. Ophthalmic examination was slightly improved in the right eye over the ensuing couple of weeks with lesion involution (Figure C). However, a small area of chorioretinitis was apparent in the left macula as well. This remained stable and may have been missed on initial examinations. She was lost to follow-up 1 month after her initial presentation.

DISCUSSION

Toxoplasma gondii is believed to be the most common cause of chorioretinitis in the United States,[1] with ocular toxoplasmosis affecting nearly 1.26 million people.[2] While 22.5% of the adolescent and adult population in the United States are seropositive indicating prior exposure,[2,3] most such individuals never develop clinical symptoms.[4] Approximately 2% of seropositive individuals in the United States develop ocular toxoplasmosis.[3,4] Infection can occur through fecal-oral transmission, needle sharing, directly from a mother to a fetus during pregnancy or childbirth, and via contaminated blood transfusions.[5] Intravenous drug users represent an interesting at-risk group for development of ocular toxoplasmosis, as one mode of transmission of the parasite is via needle sharing with an infected individual. Because the viability of infectious tachyzoites does not drop until 6 to 12 hours after exposure to the extracellular environment,[6] transmission of the parasite via needle-sharing is an important consideration. In a Chinese study, the prevalence of *T gondii* in IV drug users ranges from 17.3% to 21.8%, significantly higher than the prevalence of drug users who do not use the intravenous route in that population (7.8%, $P < 0.01$).[5] In addition, duration of IV drug use correlated with seropositivity, as 21.8% of individuals with greater than 5 years of IV drug use tested seropositive compared to 8% of those with fewer than 5 years of IV drug use.[5]

While it was previously believed that the majority of cases of ocular toxoplasmosis in adolescent and adult patients were reactivated cases of infections acquired in utero,[7] it is now established that acquired infection is more common,[1-3] with nearly two-thirds of cases acquired postnatally.[4,8] In patients with reactivated infections of ocular toxoplasmosis, there may be a history of previous episodes of blurred vision related to episodic chorioretinal inflammation.[7] Toxoplasmic serological profiles can be used to help differentiate acute from chronic infection.

Risk factors for acute acquired *T gondii* infection include eat-

ing raw ground beef; rare lamb; locally produced cured, dried, or smoked meat; working with meat; drinking unpasteurized goat milk; and having 3 or more kittens.[2,7] Patients with acute acquired ocular toxoplasmosis have a more optimistic prognosis than those with reactivation of congenital disease.[1] The severity of disease also can be affected by the immune competence of the host, the age of the host (highest risk associated with extremes of age),[3] and the genotype of the strain.[4,9]

Clinical symptoms of ocular toxoplasmosis most commonly include floaters, blurred vision, or visual loss, usually without systemic signs.[4] If present, systemic signs can include cervical lymphadenopathy or mononucleosis-like infection.[4] Ophthalmic examination typically reveals a unilateral yellow-white necrotizing retinochoroiditis with fuzzy borders[4] associated with adjacent choroiditis, vasculitis, hemorrhage, and vitreitis.[9] The primary site of infection is the retina, but the choroid, vitreous, and anterior chamber are also involved.[9] The acute inflammatory phase typically resolves in weeks to months and leaves permanent white choroidal scars with clumps of dark pigment. Often there are lesions of different ages existing simultaneously.[7] An eye examination that is suspicious for infection with *T gondii* should also prompt consideration of other pathogens such as syphilis, tuberculosis, viral-induced necrotizing retinopathies, aspergillosis, or coccidiodomycosis,[4,7] in addition to non-infectious etiologies such as Behçet's disease, multifocal choroiditis and panuveitis, and serpiginous choroiditis.[4]

Following the initial clinical exam, serology should be obtained to help establish the diagnosis. Negative enzyme-linked immunosorbent assay (ELISA) serology can help exclude toxoplasmosis; however, positive serology does not necessarily confirm ocular infection. A patient with fundoscopic exam findings that are typical of ocular toxoplasmosis who is positive for *Toxoplasma*-specific IgG and negative for *Toxoplasma*-specific IgM who responds appropriately to anti-*Toxoplasma* therapy is considered to have a reactivated form of ocular toxoplasmosis.[10] However, a patient with the above exam findings who tests negative for *Toxoplasma*-specific IgG but positive for *Toxoplasma*-specific IgM is likely to have acute disease, and further testing with intraocular fluid is recommended, though not required, to make the diagnosis.[10] It is important to note that vitrectomy with aqueous humor analysis for *T gondii* DNA using PCR carries a significant risk of ocular morbidity including cataract, retinal tear or detachment and glaucoma or ocular hypotony post-operatively. The risk of morbidity is further increased when the eye is inflamed, as it was in the case scenario described above, which is why the test was not performed on our patient even though it could have provided diagnostic confirmation.

Treatment typically consists of pyrimethamine, sulfadiazine, folinic acid, and systemic corticosteroids. Folinic acid supplementation is added to help decrease the thrombocytopenia and leukopenia induced by pyrimethamine.[9] Therapy compliance can be an issue, as the traditional regimen is nearly 10 pills per day and it is necessary to monitor blood cell counts during treatment.[4] There are other alternatives to the classic regimen including a combination of clindamycin, pyrimethamine, and corticosteroids or a combination of trimethoprim-sulfamethoxazole and corticosteroids.[9] A typical course is at least 6 weeks. For patients with contraindications to systemic therapy, intravitreal injection of clindamycin and steroids may be of benefit.[4,9] While treatment helps to control the infection and inflammation, it will not prevent recurrence,[9] and recurrence rate after treatment is 5% to 30%.[7] Long-term intermittent treatment with trimethoprim-sulfamethoxazole has been shown to decrease recurrence rates from 23.8% to 6.6%.[11] It is unknown whether recurrence of ocular toxoplasmosis is due to reactivation of infected cells elsewhere in the body carried to the eye via immune cells, reactivation of infected cells within the eye, or due to acquisition of a new parasitic infection with hematogenous spread.[8]

The patient's IV drug use was an important consideration in her care. The patient followed up with ophthalmology initially, but not with the infectious disease department. In documented phone contact, she reported not being able to make appointments due to financial and transportation issues. We do not know if or how long she took her toxoplasmosis treatment.

While it is now known that acute acquired ocular toxoplasmosis is more common than reactivated infections acquired in utero, less is known about the link between IV drug use and *Toxoplasma* infection. The role of hematogenous spread and the in vitro survival of the parasite for 6 to 12 hours following exposure to the extracellular environment suggests that IV drug users may be at considerably higher risk of acquiring infection than the general population. As mentioned above, a Chinese review notes a higher prevalence of seropositivity in IV drug users compared to drug users who do not use the intravenous route,[5] but more research is needed. It is also important to determine if people who share needles with those who have symptomatic toxoplasmosis are at increased risk for infection and if these partners should receive prophylaxis. While our patient likely acquired the infection from needle sharing with her partner, he did not have evidence of symptomatic disease, so even if clear guidelines for prophylaxis are delineated through further research, it is unlikely our patient would have met criteria for prophylaxis. In addition, if recurrent infection is in fact caused by new entry of parasites into the blood stream as one theory suggests,[8] given the high prevalence of *T gondii* in the general population it may be reasonable to infer that IV drug users would be at much higher risk of reinfection. In a prospective randomized open-labeled interventional clinical

trial conducted in Brazil, investigators found that long-term intermittent treatment with trimethoprim-sulfamethoxazole can reduce recurrence rates from 23.8% to 6.6%.[11] It is unclear how this prophylactic regimen would apply to IV drug users; however, this is an area that warrants further research.

CONCLUSION

Acute vision loss in an IV drug user has a large differential diagnosis. Infectious causes are of greatest concern, including bacterial, fungal, and parasitic etiologies (See appendix online at www.wisconsinmedicalsociety.org/publications/wmj/pdf/114/2/114no2_bettendorf_appendix.pdf). Such patients need to be treated broadly with antibacterial and antifungal agents until the diagnosis is confirmed. In addition to addressing the patient's acute vision loss, it is important to complete a full review of systems and a detailed physical exam to identify evidence that may help reach the diagnosis. Any critical findings such as this patient's meningismus must be addressed promptly as these findings may be life threatening. Acquired ocular toxoplasmosis is more common than previously thought and can be differentiated from reactivated congenital disease with *Toxoplasma*-specific IgG and IgM, as well as intraocular fluid sampling for *T gondii* DNA to confirm the diagnosis in select cases. Intravenous drug users who share needles may be at considerably higher risk of acquiring infection with *T gondii* compared to the general population, although further studies are needed to quantify this risk and determine if prophylaxis is warranted.

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Proceedings from the 2014 Annual Meeting of the American College of Physicians, Wisconsin Chapter

The following abstracts were presented during the 59th Annual Meeting of the Wisconsin Chapter of the American College of Physicians in 2014. Internal medicine residents from each of Wisconsin's 5 residency programs presented their research and/or unusual clinical experience via case- and research-based vignettes and posters. All of the vignettes as well as the winning posters are published here. Additional poster presentations are available online in an appendix and can be accessed at https://www.wisconsinmedicalsociety.org/_WMS/publications/wmj/pdf/114/2/WACP_abstracts_2014.pdf.

CASE-BASED VIGNETTES

Eosinophilic Granulomatosis With Polyangiitis (Churg Strauss Disease)

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Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg Strauss Disease, is a multiorgan disease usually affecting the lungs and skin. Patients typically present with chronic rhinosinusitis, asthma, and eosinophilia. While classically considered to be an ANCA-positive vasculitis, the sensitivity and specificity of ANCA activity level is low.

Case: A 62-year-old woman with chronic sinusitis and asthma presented with progressive shortness of breath that worsened over the past month and nodules on her fingers that developed 3 weeks prior to presentation. Outpatient use of Advair, albuterol, Spiriva, azithromycin, and steroids provided minimal relief of her symptoms. Physical exam was significant for bilateral expiratory wheezing and crackles, and papulo-vesicular nodules on the extensor surfaces of her elbows, distal interphalangeal (DIP), and proximal interphalangeal (PIP) joints. Her labs were remarkable for white blood cell (WBC) count of 12.2 with 30% eosinophils, markedly elevated erythrocyte sedimentation rate (ESR) of 116 mm/h, C-reactive protein (CRP) of 16.10 mg/dL, IgE level of 470.9 IU/mL, rheumatoid factor of 28 IU/mL. C3 was mildly elevated at 186 mg/dL. C4, total complement level, antinuclear antibody (ANA), c-ANCA, p-ANCA, proteinase 3 antibody, myeloperoxidase antibody, anti-CCP antibody, angiotensin-converting enzyme (ACE) level, urine *Histoplasma, Blastomyces,* and *Legionella* antigen were all negative. Computed tomography (CT) of chest with contrast was notable for diffuse thickening of lung parenchyma and bronchial wall, hilar, and mediastinal lymphadenopathy. To aid in diagnosis, a skin biopsy of the patient's papulo-vesicular nodules was performed and found erythema elevatum diutinum, a rare and poorly understood presentation of vasculitis. Video-assisted thoracoscopic surgery (VATS) lung biopsy revealed eosinophilic vasculitis with patchy involvement of medium-sized arteries confirming the diagnosis of EGPA. Bone marrow biopsy showed marked eosinophilia but not an increased percentage of blasts, effectively ruling out a neoplastic process leading to the hypereosinophilia. The patient was started on steroid therapy and then transitioned to a course of rituximab.

Discussion: The differential diagnosis of peripheral eosinophilia with associated skin findings included a vasculitic process such as eosinophilic granulomatosis with polyangiitis (EGPA) or sarcoidosis, neoplastic disease such as lymphoma, immunologic disease such as hypereosinophilic syndrome, or atypical infection with helminth or parasite. This case describes a typical presentation of a classic vasculitis. P-ANCA is present in only about 50% of patients with EGPA, however, our patient did not have this classical marker. In a patient with chronic sinusitis and asthma presenting with peripheral eosinophilia, clinicians must maintain a high degree of suspicion for EGPA since treatment can significantly reduce morbidity and mortality.

H1N1 Influenza A Infection as a Cause of Severe Pulmonary Complications

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Introduction: Most patients with H1N1 influenza A infection have a mild or uncomplicated clinical course. Common complications include secondary bacterial pneumonia, acute respiratory distress syndrome (ARDS), etc. Other pulmonary complications such as pneumatocele, bronchopleural fistula, and pneumothorax are very rare.

Case: A 59-year-old man, vaccinated against flu, presented with cough, fever, chest congestion, and respiratory distress. He was found to be hypoxic with bilateral alveolar and interstitial opacities on chest x-ray. Diagnosis of ARDS was made. He was intubated and started on antibiotics. Blood and sputum cultures were negative. Later, influenza A was detected on bronchoalveolar lavage (BAL). Oseltamivir was started. Follow-up CT chest showed diffuse and extensive airspace opacification and repeat

bronchoscopy was unremarkable. High dose steroids were started for fibroproliferative ARDS. He underwent tracheostomy and was eventually transferred to a long-term acute care facility. Within a month, he was admitted with shortness of breath and hypoxemia. Imaging revealed bilateral infiltrates, cavitary lesions, as well as pneumothorax. He was treated for possible health care-associated pneumonia despite negative workup and was discharged with chest tube and home oxygen. He presented to the hospital again within 3 days with shortness of breath. CT chest revealed a left bronchopleural fistula with large hydropneumothrax and persistent right pneumothorax. He underwent thoracoscopy and bronchopleural fistula repair. He had an extended hospital stay before being discharged.

Discussion: This case demonstrates the devastating complications associated with H1N1 influenza A. In our patient, the delay in diagnosis and initiation of treatment might have contributed to the development of these complications. There was no evidence of superimposed bacterial infection. Maintaining a high index of suspicion for influenza, early diagnosis, and prompt initiation of treatment is paramount in preventing complications and improving outcomes.

1st Place
Hemolytic Uremic Syndrome in an Adult Chemotherapy Patient

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Introduction: Hemolytic uremic syndrome (HUS) is often overlooked as a diagnosis in adults. Additionally, because many chemotherapy regimens are associated with diarrhea, infectious etiologies of diarrhea in cancer patients can be easily missed. The time sensitive nature of starting plasmapharesis to avoid the potentially irreversible renal damage of microangiopathic hemolytic anemia (MAHA) makes this an important diagnosis to consider, even in less classic circumstances.

Case: A 62-year-old woman on dasatinib for chronic myelocytic leukemia (CML) developed watery, nonbloody diarrhea, and nonbilious emesis without fevers during a trip to Missouri. No other family members had gastrointestinal symptoms. Her symptoms persisted for the following 2 to 3 weeks, despite a trial of loperamide and ondansetron. Upon return to Wisconsin, she was instructed to stop dasatinib and required intravenous (IV) fluids for dehydration. Her labs were notable for serum urea nitrogen (BUN) 38 and Cr2.3 thought pre-renal from volume loss. Over the next 48 hours, however, she developed worsening confusion and peri-orbital edema. Admitted to the hospital, physical exam was notable for blood pressure (BP) 159/87, pale sclera, asterixis and petechial rash on her lower back and sacrum. Labs were notable for HgB 7.8, platelets 85, BUN 49, creatine 4.82, urine analysis (UA) with 3+ protein and fractional excretion of sodium (FeNA) 1.34 suggestive of intrarenal pathology. Peripheral smear with >5 schistocytes/hpf and renal biopsy showing thrombotic microangiopathy confirmed MAHA. Stool was negative for Shigella, O157:H7, shiga toxin; however, further inquiry of outside hospital workup revealed positive stool Shigella and shiga toxin. The Missouri Department of Public Health was notified. Upon urgent initiation of plasmapharesis and intravenous immunoglobulin (IVIG), she improved dramatically over the following 6 days with normalization of cell lines and renal function.

Discussion: This case illustrates the importance of re-evaluating the cause of worsening renal function when not improving after fluid resuscitation, and remembering MAHA and HUS when presented with a history of gastrointestinal symptoms—even in adults, as early recognition and treatment are critical to maximizing renal recovery.

Heroin and Rhabdomylosis

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Case: We present a case of a 23-year-old man who was found unconscious by friends, wedged between a bed and a night stand, having been there for an unknown period of time. He was given naloxone and became transiently more responsive. Initial evaluation revealed renal failure, hyperkalemia, lactic acidosis, CPK >250,000, and absent bilateral pedal pulses. Bilateral lower extremity fasiciotomies were performed. Renal dialysis was started shortly after admission, but his metabolic acidosis and hyperkalemia continued to worsen. Bilateral above knee amputations were performed with subsequent resolution of his metabolic abnormalities. Upon wakening, the patient admitted longstanding history heroin and polysubstance abuse.

Discussion: Heroin is one of the most harmful drugs available and causes physical, emotional, and monetary burdens on both patients and society. Beyond respiratory depression and addiction, it poses many different organic problems when overdosed. In addition, narcotic addiction is a problem now reaching a younger population. Among 12 to 13 year olds, controlled prescription drugs are now the most commonly abused. In 2012, it was estimated that 10 million individuals between ages 12 and 29 needed treatment for drug addiction. Providers must become more judicious in their dispensing of addictive prescription medications knowing that they are often gateway drugs.

Rhabdomyolysis is a potentially life-threatening condition with complications including renal failure, compartment syndrome, and fatal arrhythmias. It must be suspected in any patient found down for an unknown period of time. The first line treatment of preventing these complications is heavy fluid resuscitation and frequent neurovascular checks. Although myoglobulin and its byproduct are major contributors to renal failure, the pathophysiology is much more complicated and usually is preceded by pre-renal azotemia and hyperuricemia. In a large retrospective study of patients with rhabdomyolysis, it was found that patients with pre-renal azotemia were more likely to develop renal failure versus the patients who were well hydrated.

Narcotic abuse is becoming a widespread problem taking a huge physical toll and resulting in a large economic burden as well. In Wisconsin there have been significant recent legislative efforts with the addition of resources to prevent narcotic overdose, however more needs to be done to prevent the abuse of narcotics. It requires both increased public awareness and also provider awareness across all specialties.

Monoclonal Gammopathy of Mesenteric Significance

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Introduction: Sclerosing mesenteritis, a fibroinflammatory condition of unclear pathogenesis, consists of a spectrum of uncommon disorders including mesenteric lipodystrophy and mesenteric panniculitis. Rarely, it has been reported in patients with underlying malignancies commonly of the gastrointestinal and genitourinary tracts, but rarely with leukemia/lymphomas. We present a patient with myeloma-related mesenteritis and highlight the challenges associated with nonspecific symptomatology concealing a malignant process.

Case: An 83-year-old woman with known history of monoclonal gammopathy of undetermined significance (MGUS) and previously treated stage I breast cancer developed persistent abdominal pain with eating and alternating constipation and diarrhea. CT of the abdomen showed mesenteric nodules. Recurrent breast cancer was suspected. A positron emission tomography (PET)/CT scan showed the mesenteric nodules were metabolically quiescent and no other evidence of metastatic disease, leading to the conclusion that the mesenteric changes were nonspecific. The patient continued to have symptoms for 1 year and underwent multiple endoscopies and physician visits without explanation of etiology or symptomatic benefit. She was empirically treated with prednisone 20 mg/day without relief. Subsequently, she developed bone pain in addition to her abdominal symptoms, which led to a hospitalization at our center. A PET/CT scan was repeated owing to the high suspicion for an underlying malignancy; it revealed bony lytic lesions in addition to the mesenteric nodules. Further hematology-directed workup revealed low immunoglobulin levels, however her kappa light chains of 2089mg/L (3.3-19.4 mg/L) and a free light chain (FLC) ratio of 289 (0.26-1.65). It was noted that her previous MGUS follow-up evaluation 6 months ago had shown that her FLC ratio had increased to 20.9 from a previous stable level of 9. A bone marrow biopsy confirmed multiple myeloma. She was started on treatment with lenalidomide, bortezomib, and dexamethasone with prompt resolution of her abdominal symptoms.

Discussion: Sclerosing mesenteritis includes a spectrum of disorders that lead to inflammation and fibrosis of the mesentery. Rarely, it has been associated with hematologic malignancies either as a paraneoplastic syndrome or as direct infiltration by malignant cells. In our patient, the MGUS was a clue to an underlying hematologic malignancy; the fact that it was changing as observed by an increasingly abnormal FLC ratio was a clue that it had evolved into myeloma. This case highlights the need for awareness of the paraneoplastic nature of sclerosing mesenteritis and suspicion of myeloma evolution from MGUS.

Intravascular Large B-Cell Lymphoma in a Caucasian Woman With Profound Thrombocytopenia and Dyspnea

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Introduction: Intravascular large B-cell lymphoma (IVLBCL) is an extremely rare form of non-Hodgkin's lymphoma in which malignant cells have a tropism for small- and medium-sized blood vessels. In this case, IVLBCL was diagnosed in a 78-year-old Caucasian woman who presented with severe thrombocytopenia, anemia, and progressive shortness of breath (SOB).

Case: The patient, a nonsmoker with a history of Sjögren's syndrome presented 3 months prior to admission with SOB and was told she had interstitial pulmonary fibrosis. She was treated with a prednisone taper. She returned to clinic 1 week prior to admission with bruising, dyspnea, and a platelet count of 8 K/μL. She received prednisone and gamma-globulin for presumed immune thrombocytopenia without improvement.

On admission, the patient was afebrile. Physical findings included bibasilar lung crackles, splenomegaly without adenopathy, and diffuse ecchymoses and petechiae. Labs showed a WBC 7.8 K/μL, hemoglobin 9.9 g/dL, and a platelet count of 3 K/μL. The patient's creatinine was 1.40 mg/dL, serum LDH was 1810 U/L (normal <245 U/L), and albumin was 1.9 g/dL. The blood smear showed thrombocytopenia without schistocytes. A bone marrow aspirate showed hemophagocytosis, while biopsy demonstrated monoclonal infiltrates of CD20+ lymphoid cells confined to vascular spaces, consistent with IVLBCL.

The patient was started on R-CHOP. She required daily blood products, but after 2 weeks was able to maintain a platelet count of greater than 20 K/μL unsupported.

Discussion: IVLBCL is notoriously difficult to diagnose, with more than half of cases proven at autopsy. Definitive diagnosis requires finding malignant cells in the vessels of affected organs. The disease is usually disseminated and has a variable presentation, often with nonspecific complaints, but frequently with elevated lactate dehydrogenase (LDH) and anemia. Western patients typically present with cutaneous and neurologic abnormalities. By contrast, Asian patients are more likely to have pulmonary symptoms and bone marrow involvement with thrombocytopenia and a hemophagocytic syndrome. In this case, a Caucasian patient presented with an Asian variant of IVLBCL. Prognosis is poor, but treatment with R-CHOP has improved overall survival to an estimated 60% to 80% at 3 years.

Pneumococcal Pericarditis With Tamponade

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Introduction: Pneumococcal pericarditis is a rare entity in the current antibiotic and vaccination era in the United States. Here we present a case of pneumococcal pericardial effusion with tamponade.

Case: An 82-year-old man with no significant known previous medical history was seen for fatigue of approximately 1 month's duration and dyspnea at rest for a week. He was hypotensive, tachypneic, tachycardic, and orthostatic. His exam revealed distant heart sounds, crackles in left lung base, and distended neck veins. Labs revealed leukocytosis of 197k, multiorgan dysfunction, and spontaneous tumor lysis. An electrocardiogram

(ECG) showed diffuse ST segment elevation in the anterolateral leads. Chest x-ray revealed cardiomegaly with a left retrocardiac density. Echocardiogram showed a moderate pericardial effusion with pending tamponade physiology and he underwent emergent pericardial window placement. His pericardial fluid grew *S pneumoniae.* He also was diagnosed with chronic lymphocytic leukemia (CLL), however, there were no malignant cells in the pericardial fluid. He was treated with 4 weeks of IV antibiotics with resolution of sepsis and multi-organ dysfunction.

Discussion: Bacterial pericarditis (BP) is nowadays very rare occuring, mostly in individuals with previous pericardial disease treated by chemotherapy, patients who have undergone cardiac surgery, or those receiving dialysis. Risk factors for getting BP are immunosuppression, alcoholism, and chest trauma. BP requires prompt recognition as it is life threatening and requires immediate antibiotics and surgical drainage.

Our patient's pericardial effusion initially was thought to be from his CLL until the pathology results came back negative for malignant cells. However, there has been a case report on concurrent *S pneumoniae* and malignant squamous cells in pericardial fluid. Further, negative cytology does not exclude the diagnosis of malignancy, particularly if there is a high index of suspicion. In this situation, a pericardial biopsy should be considered to confirm or exclude pericardial malignancy.

This case demonstrates the importance of considering pneumococcal pericarditis as the cause of a pericardial effusion in patients with pneumococcal sepsis and immunosuppression. Further diagnostic testing such as pericardiocentesis and culture of pericardial fluid, polymerase chain reaction (PCR), or antigen testing with early drainage is vital.

A Rare Case of Post-Infarct Ventral Septal Defect With Ventricular Pseudoaneurysm

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Introduction: Immediate mechanical complications of myocardial infarction (MI) include ventricular septal defect (VSD), papillary muscle rupture, and ventricular free wall rupture. Concomitant occurrence of VSD with free wall rupture, which gets sealed off by the pericardium forming a pseudoaneurysm, is an extremely rare and life-threatening complication of MI.

Case: A 67-year-old woman with end stage renal disease on hemodialysis was admitted for evaluation of hypotension and dyspnea. Eight weeks prior, she had a non-ST segment elevation myocardial infarction (NSTEMI) with subsequent nuclear stress test showing no reversible ischemia; she was managed medically.

Review of systems was unremarkable, except for worsening lower limb edema. Physical examination was significant for a blood pressure of 71/54 mmHg and 3+ leg edema. Cardiac exam was notable for a pansystolic murmur. Chest x-ray revealed a moderate right pleural effusion.

Echocardiogram demonstrated severely reduced right heart function, markedly different from her previous echocardiogram. Chest CT, performed to rule out pulmonary embolism, revealed a focal outpouching along the inferior interventricular septum with possible communication between ventricular cavities, suspicious for VSD associated with an aneurysm. Transesophageal echocardiogram (TEE) and magnetic resonance imaging (MRI) confirmed the diagnosis. Coronary angiography revealed 100% occlusion of the right coronary artery (RCA), supporting the post-infarct etiology. Given the patient's comorbidities, a percutaneous approach of VSD occlusion was adopted. The patient had an uneventful postintervention hospital course.

Discussion: Ventricular free wall rupture is a serious complication of MI. Rupture of the inferior wall contained by the pericardium forms a pseudoaneurysm. Patients can be asymptomatic or present with chest pain and hypotension. A high index of suspicion is necessary for early diagnosis. Associated with VSD, it can lead to significant hemodynamic instability and cardiogenic shock. When feasible, a surgical approach is preferable and can be lifesaving.

A Rare Cause of Seizures

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Introduction: Anaplasmosis is rarely associated with neurologic manifestations other than confusion. Rarely, meningoencephalitis has been associated in immunocompromised hosts. Anaplasmosis-associated seizures have not been reported. Described below is a man afflicted with seizures after infection with *Anaplasma phagocytophilum.*

Case: An 81-year-old man from northern Wisconsin presented to his primary care provider with progressively worsening generalized myalgias and weakness with increasing frequency of low-energy falls of 3 weeks duration. These were accompanied by fevers, chills, anorexia, headache, and lightheadedness during the week prior to presentation. Two weeks prior to presentation, he was bitten by a tick and was unable to remove all of it until he was seen by dermatology the next day. He did not develop a rash. Physical exam revealed an afebrile, pleasant, ill-appearing man and no other abnormalities. Initial lab studies revealed leukopenia, thrombocytopenia, and borderline elevated alanine aminotransferase (AST) and alanine aminotransferase (ALT). CRP was 5.0, ESR was 8. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) IgM antibodies were negative. Lyme serology was negative. PCR detection was positive for *Anaplasma phagocytophilum* DNA and negative for *Babesia* and *Ehrlichia* species. ECG and chest x-ray were normal. He was treated empirically with doxycycline. He developed a fever of 103° on hospital day 2 but was otherwise stable. His symptoms improved and discharge was planned. On hospital day 4, he developed acute confusion without other focal neurologic deficits. He developed a tonic-clonic seizure of 1 minute in duration while in CT scan. CT head was normal. He was placed on continuous electroencephalogram (EEG) monitoring and started on levetiracetam. Brain MRI was normal. Lumbar puncture was unremarkable and PCR was negative for Lyme, Arbovirus, West Nile virus, herpes simplex virus (HSV), and varicella zoster virus (VZV). He continued to have intermittent epileptiform activity until he was switched to divalproex sodium and

his condition improved. He was discharged home with doxycycline and divalproex sodium. He had no seizure recurrence and his antiepileptic was weaned off.

Discussion: Anaplasmosis has been a reportable disease since 1999, with over 1600 cases reported in 2010. It is transmitted via the Ixodes scapularis tick in the north central and northeast regions of the United States. After an incubation period of 1 to 2 weeks, symptoms of fever, malaise, myalgias, and headache develop. Rash occurs infrequently. More severe symptoms include shock, rhabdomyolysis, and renal failure. Neurologic manifestations such as meningoencephalitis have been documented but are extremely rare. Recommended management is with doxycycline, which has low but adequate cerebrospinal fluid (CSF) penetration for treatment of neurologic disease.

Seronegative Granulomatosis With Polyangiitis Presenting as a Lung Mass

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Introduction: Granulomatosis with polyangiitis (GPA) is a vasculitis with systemic manifestations mainly in respiratory and renal systems. Rarely it involves other systems, (eg nervous, cardiovascular, and genitourinary systems).

Case: A 49-year-old man presented with sinus discharge and intermittent headache for 1 year. He was treated initially with oral antibiotics without improvement and subsequently developed epistaxis. MRI of the head showed faint enhancement of the extracranial right mastoid facial nerve and paranasal sinus mucosal disease. Upper airway examination revealed significant sinonasal inflammation with scarring out of proportion to regular sinus infection. Two months later he began to cough. Imaging studies revealed consolidation in the right upper lobe with a possible mass. He was treated for pneumonia with ceftriaxone. Follow-up CT scan revealed new cavities formation. Myeloperoxidase-antinuclear cytoplasmic antibodies (MPO-ANCA) and proteinase 3- antinuclear cytoplasmic antibodies (PR3-ANCA) were both negative. Kidney function and urinalysis were normal. Bronchoscopy with transbronchial and endobronchial biopsies were not diagnostic. Right upper and middle lobectomies with lymph node sampling showed necrotizing granulomatous inflammation with geographic necrosis and vasculitis, which was consistent with GPA. He was started on high-dose corticosteroids and received 2 cycles of rituximab with significant improvement of his respiratory symptoms. He currently is being weaned of corticosteroids and transitioned to azathioprine.

Discussion: This case demonstrates the importance of considering GPA in patients with recurrent sinus symptoms combined with lower respiratory tract symptoms in spite of negative serologies. Early diagnosis and treatment is important to prevent mortality and organ loss. MPO-ANCA and PR3-ANCA antibodies are positive in 82% to 94% of the patients. Ten percent of patients with GPA can be serongative. The diagnosis must be confirmed with biopsy, which can be obtained from the target organ.

RESEARCH-BASED VIGNETTES

Development and Validation of a Risk Score to Predict Access Site Complications After Peripheral Vascular Interventions

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Purpose: Access site complications (ASC) after peripheral vascular interventions (PVI) are associated with prolonged hospitalization and increased mortality. The aim of this study was to create a clinical scoring tool to stratify patients according to their risk of developing post-PVI ASC.

Methods: The Society for Vascular Surgery Vascular Quality Initiative database yielded 27,997 patients who had undergone PVI from July 2007 to January 2014 at 151 North American centers. Clinically and statistically significant ($P < 0.05$) preprocedural risk factors associated with in-hospital post-PVI ASC were included in a multivariate logistic regression model with ASC as the outcome variable. A predictive model was developed with a random sample of 70% of the dataset and validated against the remaining 30%. Risk factors were assigned weighted integers based on their beta coefficients, and the sum constituted the risk score.

Results: ASC occurred in 939 (3.4%) patients. Predictors included were female gender, age >70, white race, bedridden ambulatory status, insulin-dependent diabetes mellitus (IDDM), prior minor amputation, procedural indication of claudication, and non-femoral arterial access site (model c-statistic = 0.637). The discriminatory power of the risk model was confirmed by the validation dataset (Brier score = 0.033). Higher risk scores correlated with increased frequency of ASC: 1.9% for low risk (score 0-15), 3.4% for moderate risk (16-27) and 5.0% for high risk (28-34).

Conclusions: The proposed clinical risk score based on 8 preprocedural characteristics is a simple tool to stratify patients at risk for post-PVI ASC. The risk score may assist physicians in therapeutic decision-making, including selection of the appropriate bleeding avoidance strategy, to improve outcomes in patients undergoing PVI.

Factors Affecting Specimen Accrual in a Community Hospital Biobank

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Background: Community hospital biobanks are important contributors to several cancer genome programs. In an effort to improve the specimen accrual, we sought to determine cancer patients' attitudes and knowledge about donating tissue for research.

Methods: We mailed questionnaires to 500 patients who had undergone cancer surgery at our hospital in the year 2012.

Results: Response rate was 43.4% (217/500). Only 36/217 respondents were aware of the biobank (BB), 32 of whom had consented to tissue collection. Of the 181/217 who were not aware, 120 believed that they would have consented had they been aware, 46 were not sure, and 15 would have refused. Most respondents (174/217) saw possible benefit for others as the most important reason for consenting. Forty-one of 217 patients

believed there is a potential for misuse of their tissue or personal information, 17 did not want to deal with any extra issues, and 11 did not understand the concept. None cited religious or cultural beliefs as factors influencing their decision.

Conclusions: The majority of the people were unaware of the concept of BB but if made aware, most of them would have consented primarily to help other cancer patients. Lack of patient awareness is an important difference between a smaller community hospital and a bigger quaternary setting. With increasing participation of smaller centers towards international cancer genome programs, improving patient awareness could be a major step in increasing specimen accrual. Despite being unaware, most patients showed good understanding of the concept of BB. The fear of misuse or commercial use of their tissue and personal information was their biggest apprehension. Hence, even a small, informative conversation addressing this issue could help allay patient fears about tissue donation.

The Novel P13K/Akt/mTOR Inhibitor Palomid 529 Can Inhibit Human Lung Fibroblast Differentiation in an In Vitro Model of Idiopathic Pulmonary Fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) is a fibroproliferative lung disease with very few therapeutic options. Investigation was made into whether the PI3K/Akt/mTOR inhibitor Palomid 529 (8-[1-hydroxyethyl]-2-methoxy-3-[4-mehtyoxybenzyloxy]-benzo[c]chromen-6-one), which is a target of both mammalian target of rapamycin complex 1 (mTORC-1 and mTORC-2) could inhibit fibrosis in human lung fibroblasts in an in vitro model.

Treatment of human lung fibroblasts after stimulation with transforming growth factor beta (TGFß) with differing concentrations of P529 led to concentration-dependent reduction of fibrotic proteins in the form of smooth muscle actin, fibronectin, and collagen-1 as well as reduction in the protein kinase B (Akt) pathway by decreasing the amount of phospho-Akt (pAkt) via Western blotting after 24 hours of treatment. Moreover, there appears to be a reduction in the cofilin pathway with a decrease in the amount of phosphcofilin (pcofilin) as well. P529 was compared against dimethyl sulfoxide (DMSO) as well as negative control. Luciferase assays were performed to investigate protein transcription. Immunohistochemical methods on human lung fibroblasts investigated the proliferation of human lung fibroblasts with differing concentrations of P529.

These preclinical in vitro observations are promising as the mTOR pathway could be a target for future IPF research and that the PI3K/Akt/mTOR inhibitor P529 should be further explored as a candidate treatment for IPF.

Providers' Experience With Sex Trafficking Victims

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Background: Though many health care providers come into contact with victims of sex trafficking, very few recognize and identify the victims, resulting in potentially significant health disparities for this vulnerable population. One study found that 28% of victims were seen by a health care provider during the time they were being trafficked. Sex trafficking (ST) victims are a unique subset of patients with specific identification and needs. Our objective was to evaluate knowledge gaps and training needs of medical providers, importance of training for a victim's specific needs, as well as barriers to the identification and response to victims.

Methods: Survey of 168 health care workers including physicians, nurses, nurse practitioners, physician assistants, social workers, and patient/family advocates at multiple hospitals and medical clinics in urban, suburban, and rural locations. In particular, we focused on specialties and locations that would likely encounter victims, such as social work, general pediatrics, adolescent medicine, child abuse pediatrics, internal medicine, emergency medicine, obstetrics and gynecology, sexual assault nurse examiners, and urban free clinics. The survey was sent to the chairs of each of these departments for distribution to potential participants.

Results: In 2 clinical vignettes, only 48% correctly classified a minor as a ST victim, and only 42% correctly distinguished a ST victim from a child abuse victim. Of respondents, 62.5% said that they had never received training on how to identify ST victims. Those with training were significantly more likely to report ST as a major problem locally ($P < 0.001$), to have encountered a victim in their practice ($P < 0.001$), and to have greater confidence in their ability to identify victims ($P < 0.001$). The greatest barriers to identification of victims reported were a lack of training (34%) and lack of awareness (21%) on ST. There also were many action steps taken once a victim was identified, which included calling child protective services (69%), contacting local police (66%), referring patient to human trafficking victims' services (42%), and calling the national hotline (31%).

Discussion: Health care providers demonstrate a lack of knowledge and awareness of ST that correlates with their limited experience and training. Training is vitally important to improve identification of these victims and provide appropriate care for their specific needs. There is also a need for a coordinated, uniform protocol, without which many health care workers are not confident in their ability to connect patients with the necessary services. Consequently, this may affect their willingness to screen potential victims.

1st Place

Repeat Lipopolysaccharide Exposure is Sufficient to Impair Viral-Induced Pro-atopic, CD49d Expressing Neutrophil Recruitment to the Lung

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Background: Severe respiratory viral infections increase the risk of developing asthma and atopic disease. In the Sendai virus (SeV) mouse model, we demonstrated this risk depends upon the early recruitment of CD49d expressing neutrophils to the lung. We also demonstrated that single intranasal (i.n.) dose of lipopolysaccharide (LPS) prior to SeV infection significantly reduced

CD49d+ neutrophils in the BAL. The hygiene hypothesis suggests chronic microbial exposure prevents development of atopic disease. Our study investigated whether chronic LPS exposure would reduce SeV mediated CD49d+ neutrophil recruitment to the lung and BAL.

Methods: C57BL6 mice were treated with daily LPS (3 μg) i.n. starting 1 or 3 days before or with SeV infection (day 0). On day 3 post SeV, the BAL and lung were isolated and the frequency of CD49d+ neutrophils determined by flow cytometry.

Results: In the BAL, CD49d+ neutrophils were reduced most significantly when LPS exposure was started 1 day prior to or the day of SeV infection (23.6±1.8%, 10.2±1.6% [0.0002], 10.5±2.2% [0.0037], 17.4±3.6% [0.11]; mean ± sem percent CD49d+ neutrophils [*P* value vs PBS] for PBS, LPS starting on day 0, -1, or -3; n≥3). In the lung, CD49d+ neutrophils decreased regardless of LPS starting day (42.9±3.7%, 18.7±2.0% [0.0003], 22.6±1.0% [0.013], 24.9±2.0% [0.0052]; n≥3).

Discussion: Chronic LPS exposure reduces SeV mediated CD49d+ neutrophil accumulation in the lung and the BAL, suggesting an interaction between the viral and hygiene hypotheses in driving atopic risk. Future studies will explore whether chronic LPS exposure is sufficient to prevent the development of postviral atopic disease.

DISPLAYED POSTERS

1st place

A Rare Case of Delirium Associated With Crowned Dens Syndrome

Anne S. Yu, MD, Trusha Patel, MD, Lawrence Ryan, MD, Medical College of Wisconsin, Milwaukee, Wis

Introduction: Crowned dens syndrome (CDS) is a rare and under-recognized cause of acute neck pain. CDS is characterized by severe cervico-occipital neck pain associated with deposition of calcium pyrophosphate dihydrate (CPPD) around the odontoid process (or dens) to give the appearance of a crown on imaging. Because CDS often is associated with neck stiffness, fever, and elevated inflammatory markers, it can be misdiagnosed as other conditions such as meningitis, cervical spondylitis, or polymyalgia rheumatica, thus delaying diagnosis and appropriate treatment.

Case: An 87-year-old man with history of hypertension, diabetes, and chronic kidney disease presented with acute delirium on top of gradual cognitive decline. The patient's family noted increased confusion and severe neck pain in the past week. On exam, he had fever to 101ºF and was oriented only to self. He had significant neck tenderness and stiffness with restricted cervical range of motion but no focal neurological deficits. He also had active synovitis to the bilateral knees and wrists. Labs revealed normal white count and elevated acute phase reactants with sedimentation rate of 82 mm/h and C-reactive protein 22.8 mg/dl. Infectious workup with urinalysis, blood cultures, and chest radiography were negative. A lumbar puncture was attempted but unsuccessful. Due to the patient's persistent severe neck pain, CT and MRI cervical spine were performed, revealing calcium deposition around the odontoid process, consistent with crowned dens syndrome. Left knee arthrocentesis was subsequently performed with CPPD crystals on synovial fluid analysis suggestive of acute pseudogout. The patient was started on prednisone 30 mg daily with subsequent taper for treatment of crowned dens syndrome related to CPPD and polyarticular pseudogout with rapid and significant improvement in mental status and neck and joint pain.

Discussion: Crowned dens syndrome can present with a pseudo-meningitis picture with acute neck pain and fever. CT of the cervical spine is the gold standard imaging modality with classic finding of calcium deposition in a crown around the dens. The majority of patients with CDS also have chondrocalcinosis with CPPD deposition within primary sites (eg, knees, wrists, ankles). Treatment consists of NSAIDs or steroids, with dramatic improvement in symptoms and excellent prognosis. Thus, CDS should be considered in the differential with this clinical picture to avoid unnecessary invasive procedures and allow for appropriate diagnosis and rapid initiation of targeted treatment.

2nd place

Left Ventricular Noncompaction: Etiology, Pathology, and Clinical Significance

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Case: A 29-year-old African American man presented with clinical symptoms of congestive heart failure with unclear etiology. When he came to the emergency department for an abdominal gunshot wound at the age of 22, he was incidentally diagnosed with severe left ventricular (LV) dilation and heart failure (HF). His left heart catheterization was negative for acute coronary disease to explain his systolic dysfunction. He had an ejection fraction of about 20% and had an AICD placed. In addition, he was unaware of any family history of cardiovascular disease.

During this admission, the patient complained of increasing dyspnea on exertion, paroxysmal nocturnal dyspnea, weight gain, and feeling as though his implantable cardioverter-defibrillator (ICD) had fired. He was diagnosed with congestive heart failure exacerbation secondary to poor diet and medication non-compliance. He was diuresed and TTE was performed. TTE showed trabeculation seen within the LV endocardium concerning for left ventricular noncompaction (LVNC). Furthermore, a small thrombus within the trabecaulation could not be ruled out.

LVNC, also known as spongy myocardium, is a rare disease that occurs in the 12th week in utero when the spongy myocardium fails to transform into mature compact myocardium. This results in deep recess and trabeculations that form within a dilated left ventricle. This is a rare disease but should be considered in the differential for diagnosis of new onset HF in young individuals.

These individuals are at an increased risk for arrhythmias, thrombus formation, and heart failure. The diagnosis is made either by TTE or cardiac MRI (not performed on this patient given that he had a subcutaneous ICD lead). Anticoagulation should be considered given their increased risk for thromboemboli caused by their dilated left ven-

tricle. Our patient was started on coumadin given potential for LV thrombus formation. This is also a congenital disease, so family members should be offered an opportunity to be screened. This did not occur in this case because of the patient's financial constraints. Keeping LVNC in the differential for new HF in younger individuals is critical as it helps clinicians risk stratify the patient's outcomes for strokes, arrhythmias, and their children's risk for heart disease.

3rd place

Case Report of an Aggressive Lymphoma With Mixed Plasma Cell and T Cell Features in a Patient With Crohn's Disease Receiving Tumor Necrosis Factor Alpha Inhibitors

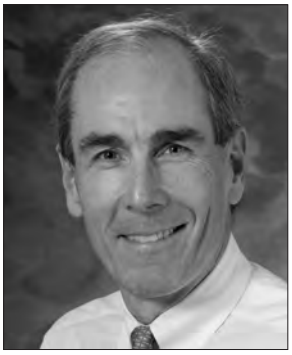
Sameer Tolay, MD, Yogita Fotaria, MD, John P. Farnen, MD; Gundersen Medical Foundation, La Crosse, Wis

Case: A 62-year-old man with Crohn's disease presented with fever, drenching night sweats, and increased frequency of watery diarrhea. He also reported severe anorexia, cachexia, and weight loss. This was his 5th hospital admission in past 30 days with similar symptoms. He had multiple laparotomies in the past, with a total of 128 cms of small bowel removed to date. Due to disease progression, initially on methotrexate and later adalimumab, he had recently started on a combination of 6 mercaptopurine (6 MP) and certolizumab. He underwent colonoscopy, which showed mild active disease at the anastomotic site with normal C- reactive protein on all admissions. Biopsy was negative for cytomegalovirus and inclusion body disease. His stool cultures repeatedly had come back negative for routine bacteria, ova, and parasites including *Giardia* and *Cryptosporidium.* Other tests that had come back negative were serum HIV, EBV, hepatitis panel, cryptococcal antigen and fungal assays. Six MP levels were found normal as well, and discontinuation of this drug did not improve his symptoms. His symptoms were persistent despite empirical treatment with steroids for Crohn's flare and use of cholestyramine.

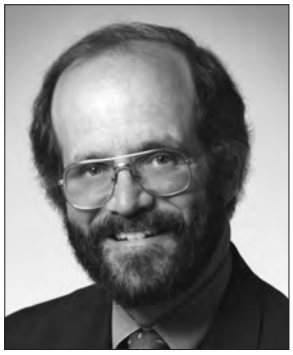
Physical exam during this admission revealed left axillary adenopathy and a 2 cm x 2 cm erythematous skin lesion on his scalp. He also was found anemic with hemoglobin of 9; lactate dehydrogenase was mildly elevated at 400. CT scan of abdomen showed a left flank mass measuring 6 cm x 6 cm with mild splenomegaly and mesenteric adenopathy; the latter also was noted on MRI 2 years prior and was thought to be reactive at that point. Biopsy of the left flank mass showed an unusual combination of cell surface markers with presence of both T cell (CD 3) and plasma cell (CD 38, 138 and Mum 1) markers. This sample was sent for second opinion at a quaternary center where findings were confirmed and was diagnosed as "aggressive plasmablastic lymphoma with aberrant expression of T cell markers." Bone marrow and CSF analysis came back negative for lymphoma. Biopsy of scalp lesion revealed squamous cell skin cancer. Patient opted for comfort care after carefully evaluating all his treatment options and expired peacefully within 2 to 3 days.

Discussion: The activity of tumor necrosis factor alpha (TNF) against tumors in laboratory models and, potentially, in humans raises the possibility that tumor necrosis factor alpha inhibitors (TNFI) might potentiate the clinical risk of malignancy. There are studies supporting increased incidence of cancers, especially skin cancer and lymphoma in patients receiving TNFI, but their accuracy is questionable due to mixed patient population and frequent coadministration of immunomodulators like 6 MP and azathioprine, which also are implicated in the causation of lymphoma. Thus, a more homogeneous sample consisting of patients with Crohn's disease treated solely with TNFI is needed to reach accurate results. Our patient's unusual lymphoma with rare atypical characteristics and presence of a concomitant squamous cell skin cancer makes us strongly suspicious of TNFI playing a role in the pathogenesis of these cancers.

K. Craig Kent, MD,



Eugene F. Foley, MD



Robert N. Golden, MD

Rural Surgery—A Crisis in Wisconsin

K. Craig Kent, MD; Eugene F. Foley, MD; Robert N. Golden, MD

Although great emphasis has been placed on the shortage of primary care physicians in this country, an equally important and looming crisis is the deficit of rural general surgeons.[1] For a small community, the loss of its general surgeon can be devastating. This issue is particularly acute in Wisconsin, where there are many small communities and multiple critical access hospitals spread over a large geographic area. Many of the approximately 500 general surgeons in Wisconsin currently practice in rural environments. However, trainees from Wisconsin surgical programs often do not choose rural practice. In 2011-2012, although there were 24 positions available in Wisconsin for rural surgeons, 12 of the 16 graduates of general surgical residencies sought specialized fellowships.[2] These numbers exemplify the mismatch between the supply and demand for rural general surgeons. They also are the reason the University of Wisconsin School of Medicine and Public Health's (UWSMPH) Department of Surgery created an innovative Rural Residency Training Track, as described below.

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Doctor Kent is the A.R. Curreri Professor of Surgery and chair of the University of Wisconsin School of Medicine and Public Health (UWSMPH) Department of Surgery; Dr. Foley is professor of surgery, vice chair of clinical operations for the Division of General Surgery, and director of the General Surgery Residency Program; and Dr. Golden is the dean of the UWSMPH, Robert Turell Professor in Medical Leadership, and vice chancellor for medical affairs, UW-Madison.

Why Is Rural Surgery Unattractive?

While many small communities have the resources and population to support a single surgeon, it is rare to find individuals willing to take the 24/7 call associated with solo practice. Some surgeons overcome this by developing partnerships with surgeons from neighboring communities, but this creates the burden of covering multiple hospitals that may be many miles apart.

Also, for surgeons who have trained in an urban environment, the transition to rural life can be challenging for both the surgeons and their spouses. Rural hospitals, comparatively, have limited technology and related infrastructure, and this may preclude the surgeons' abilities to perform some procedures that represent the mainstay of general surgery training. Alternatively, rural surgeons often are called upon to perform interventions that are not emphasized during general surgery residency, including endoscopy, colonoscopy, C-section, obstetrics, hand surgery and urological interventions. The average general surgeon performs 23 different operations, and this spectrum is even greater for surgeons who practice in rural environments.[3] Moreover, the economics of running a private solo or small group practice in today's health care environment have become challenging.

Finally, most general surgery residents do not have significant exposure to surgeons who can serve as role models for careers in rural surgery. These many factors have caused a precipitous drop in the number of general surgery residents willing to embark on a career in rural surgery.

Why Should Rural General Surgery Be Preserved?

Obtaining surgical care far away from home is disruptive for patients and their families. For specialized care, this may be necessary. However, routine surgical care can and should be provided locally, in a way that is more efficient, less costly and more desirable for the patient.

Furthermore, the importance of rural surgeons to the economic stability of small hospi-

tals and rural communities can be substantial. Surgical procedures often produce the critical margin that sustains the fragile economics of a critical access hospital. Moreover, in many small communities, the local hospital is the largest employer. Finally, the practice of rural surgery can provide an exceptionally rewarding career for the right individual. Rural surgeons enjoy substantial independence, and in an era of increasing specialization, they retain the ability to perform a wide variety of surgical procedures. Surgeons who enjoy highly satisfying careers in rural practice draw a sense of deep fulfillment from their many positive contributions to the health and vitality of their communities.

Solutions

While several issues have contributed to the rural surgery crisis, key aspects of surgical training are among the prime factors.[4-6] Most medical students who are interested in rural surgery find themselves in university-based surgical residencies in urban environments, where the focus is on highly specialized and complex surgery. Without exposure to and mentorship from rural community practitioners, these individuals will most likely seek fellowships after their residencies to gain further specialization. Seven years later, they likely have long forgotten their prior aspirations to develop careers in rural surgery.

We believe that university-based programs such as ours must develop novel strategies to address this crisis. To that end, in 2014 we created an innovative Rural Residency Training Track. This program, which is accredited by the National Resident Review Committee in Surgery, offers a new and distinct categorical position called "UW Rural Residency."

The new program's curriculum differs from our standard surgical training. It incorporates rotations that are designed to broaden the trainee's expertise in surgical areas essential to small community practice, including additional rotations in endoscopy/colonoscopy, ENT, orthopedics, urology, and gynecology. It provides a major focus on trauma and emergency general surgery. Importantly, 18 months of the 5-year program will be devoted to rotations throughout Wisconsin. These rotations will immerse trainees in the rural surgical environment and give them the opportunity to develop mentored relationships with community general surgeons. We have created partnerships with surgical practices in Neenah and Waupun, Wisconsin, and are discussing additional relationships.

Selection criteria for this track will be rigorous, and it will be essential that prospective trainees demonstrate passion for careers as rural surgeons. We are recruiting our first resident for this program, and that person will begin training in July 2015. More than 100 applicants with declared interest in rural community practice have applied for that 1 position.

We believe this innovative rural surgery track will create a cohort of new surgeons with the breadth of skills necessary to launch successful careers in rural practice. The trainees' immersion in rural environments and their exposure to outstanding community-based role models during the critical years of residency training should solidify their vision of highly satisfying lives as rural surgeons.

Table 1: Grant Support

The first two grants listed below are designed for program development.
The last one will pay the salary/benefits of the first 3 residents for their entire 5 years of clinical training.

1. Title: Development of a Rural Surgery Residency Training Program.
Sponsor: Wisconsin Rural Physician Residency Assistance Program (WRPRAP)
Dates of Award: July 1, 2013-July 1, 2016
Total Award: $375,000
PI: Eugene F. Foley, MD

2. Title: Development of a Rural Surgery Residency Training Program
Sponsor: Wisconsin Department of Health Services
Dates of Award: June 1, 2014-June 1, 2017
Total Award: $530,000
PI: Eugene F. Foley, MD

3. Title: Rural Surgery Residency Training Program, Stipend Grant
Sponsor: Wisconsin Department of Health Services
Dates of Award: July 1, 2015-June 30, 2022
Total Award: $1,125,000
PI: Eugene F. Foley, MD

Abbreviation = PI, principal investigator

Summary

Recruitment of general surgeons to practice in rural environments is challenging. We believe that innovative training programs focusing on the specific needs and experiences of rural surgical practice can play an important role in addressing this clinical workforce issue. For practical reasons, our program will start out small, but if 50 centers around the nation were to establish a similar rural track, we could see a substantial collective impact over time. We hope our new program will serve as a model for the development of other university-based residency training programs with similar opportunities.

We are grateful to have received state funding to support the development and early implementation of this program (see Table). We commend the state for understanding the importance of primary care surgery, and we look forward to measuring and reporting the impact of our rural training program on rural surgical care in Wisconsin.

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Preventing Adverse Drug Events

Jay A. Gold, MD, JD, MPH

Adverse drug events are a leading cause of preventable patient harm. An adverse drug event is defined as an injury resulting from medical intervention related to a drug. With an increasing number of patients taking prescription medications and seeing multiple providers, medication safety in all health care settings is essential to care coordination and improving the health of patients. Improving medication safety and coordination of care can prevent adverse drug events, increase patient engagement, and thereby reduce harm.

MetaStar, as part of its work with its Michigan and Minnesota counterparts in the Lake Superior Quality Innovation Network to improve care for Medicare beneficiaries, is working with Wisconsin providers to increase medication safety. The aim is to reduce and prevent adverse drug events by implementing proven best practice strategies, using tools that align with the US Department of Health and Human Services National Quality Strategy and the Health and the Human Services National Action Plan for Drug Event Prevention, along with other national, state, and local initiatives.

Within certain defined communities in the state, MetaStar will recruit those who serve beneficiaries who are taking 3 or more medications, including at least one of the following high-risk medications: anticoagulants, diabetic agents, and opioids. We will involve pharmacies within the community, including retail pharmacies, ambulatory pharmacies, hospital pharmacies, and long-term care pharmacies, as well as clinical pharmacists who are providing care in an ambulatory or long-term care setting. We will partner with the Pharmacy Society of Wisconsin, the national Alliance for Integrated Medication Management collaborative (AIMMc)[1], Wisconsin's schools of pharmacy, and national pharmacy organizations.

As part of this project, MetaStar and our partners in the Lake Superior Quality Innovation Network will provide medication safety training to providers, including proven strategies for medication therapy management, medication reconciliation post-discharge, and safety measures directed specifically to anticoagulant, diabetic, and opioid medications. We will provide specific training on evidence-based toolkits and strategies to reduce and prevent adverse educational activities and resources to promote engagement of beneficiaries and their families.

The success of the project will be measured by the decrease in adverse drug events for Medicare beneficiaries in our communities who are being screened for such events.

For physicians, important things to keep in mind in order to minimize adverse drug events are:

- *The importance of screening.* All patients should be assessed for adverse drug events, to see if any recent problems on their problem list are being caused by prescribing a larger dose than necessary, interactions with other medications, or the use of a high-risk medication when a lower risk one could do the job. A tool like the Medication Therapy Intervention & Safety Documentation Form developed by Steven Chen, PharmD, of the University of Southern California, may be useful.[2,3]
- *Looking for potential adverse drug events.* It is possible not only to look for adverse events that already have taken place, but for near misses as well. Doctor Chen's tool can be useful for this purpose.
- *Root cause analysis.* Once actual or potential adverse drug events are discovered, look at why they happened. Perhaps some of them constitute a pattern. Or perhaps lessons can be learned from individual cases that can head off future adverse events.
- *Avoid the "prescribing cascade."* Sometimes an adverse drug reaction is misinterpreted as a new medical condition and another drug will be prescribed, which both fails to deal with the root problem and places the patient at risk of additional adverse effects.
- *Medication reconciliation.* The physician plays an important role in verifying the patient's current medications and medication history, ensuring that the medications and doses are appropriate, and documenting changes in medication orders.
- *Making use of your pharmacist.* For hospital patients, or if you have patients in other settings that have in-house pharmacies, involvement of the clinical pharmacist in analysis of adverse events and in medication reconciliation can be most valuable.

If you have any questions about MetaStar's medication safety project, please contact Jay A. Gold, MD, JD, MPH, MetaStar's Chief Medical Officer, at 608.274.1940 or jgold@metastar.com.

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