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Thank You

By Tom Hermann, MD
SDSMA President

As my year representing you as your South Dakota State Medical Association (SDSMA) president comes to a close, many thoughts come to mind of whom to thank. I want to tell you all what an amazing and dedicated team of leaders you have chosen to work for you, and yes, I wish to express my appreciation to all of you for the honor to serve you this past year.

First of all, I thank my wife, Terry, for her enduring support and effort to help me time manage and for her reminders to get things done.

A special thanks to our SDSMA staff, and leader, Barb Smith, for doing everything that this special group does. They run our office and guide us in serving physicians, they organize our efforts, and all the memos and communications to stay on top of things – accolades.

To my dedicated Executive Committee team, high fives all around for participating diligently and thoughtfully regarding everything that’s needed to guide our association through the complex matters that invariably come forward.

Thank you to my clinic and hospital leadership and my practice partners, for allowing me the time away.

Thank you to my patients and my Sturgis families who let me know how special it was for them to have me represent medicine in our state, and to our University of South Dakota Sanford School of Medicine leadership and students who delight and challenge me to be a better teacher and colleague. To our SDSMA past presidents and leadership on the Council of Physicians and district medical societies across the state – thank you. Your interest and input are invaluable regarding our advocacy efforts and the heart and soul issues surrounding the practice of medicine going forward. Thank you to our teachers for their efforts in our medical school and for their support for South Dakota Medicine as they continue to strive for and produce excellence in scholarship and guidance to our medical community.

Thank you to our American Medical Association (AMA) delegates Mary Carpenter, MD, and Rob Allison, MD, for their passion and commitment representing us and their work to guide our students who attend to learn about national advocacy, political issues, and the democratic process of our AMA.

This year we have seen the transition of our SDSMA from a guiding ownership interest and role involving DakotaCare to a transition of new ownership by Avera and the necessary separation of business services and office arrangements long shared between DakotaCare, SDSMA, and the South Dakota Foundation for Medical Care.

Our association’s governance has taken on new bylaws, and this June the Executive Committee will become a board of directors. Our former Council of Physicians will become a Policy Council, responsive to issues and policy guidance, providing quick feedback to our board of directors. This new structure accomplishes and supports the mission of our SDSMA. Our membership will see the leadership listening and functioning well on their behalf. I have confidence in our team.

Some of my previous columns have mentioned our “circles of care being unbroken” and “our cups of medical practice being more than half full” as we together strive to adapt to changes in the future of the business of medicine while maintaining the special ideals of the patient-physician relationship and the profession of medicine.

We are all honored to serve our patients. As we do so, we likewise honor our teachers and mentors before us. As we continue to support our SDSMA, we share a special unity of commitment to the quality of medicine and practice. As such, our AMA and SDSMA House of Medicine seek to include all our specialty societies so important to all of us for education; shared insights into practice issues; and policies facing our practices, clinics and hospital systems. Together we have a stronger voice, and this unity makes our shared advocacy efforts more meaningful and successful. We will not always be right, but as a team we will listen, strive to get it right, and represent you well. Please continue to support each other as physicians by supporting your SDSMA.

Thank you again for the privilege to have served you as your SDSMA president this past year. I know I was just part of your amazing leadership team.
“To Live, to Love, to Learn, to Leave a Legacy.” That subtitle of a book by Stephen R. Covey provides insight into our lives. Why is that last part so difficult? People’s eyes light up when they talk about how they want to impact the world, but mention estate planning, which is essentially preparing for the transfer of your “wealth” measured in financial and other terms, and, too often, the conversation crashes.

Almost everyone realizes the importance of planning, yet according to the American Bar Association, fifty-five percent of Americans die without a will or estate plan\(^1\). Why the disconnect? Frequently cited reasons include aversion to talking about mortality, pervasive busy-ness leaving not enough time to plan, complexity, and even lack of awareness of having planning needs.

Do not fall into the trap. Ben Franklin wisely said, “An ounce of prevention is worth a pound of cure.” That 16:1 ratio might literally be accurate. A recent study estimates nationwide probate costs at $2 billion annually.\(^2\) Talk to someone cleaning up their parent’s unplanned estate. Listen to a devastated young family dealing with the aftermath of an unexpected death. “Costs” are not always measured in dollars.

Work with your advisor or attorney to get your plan in place. Commit to getting a will or trust in place. Ensure your finances are transferred according to your wishes. Protect your assets from unforeseen creditors. And, certainly for young families, provide for and protect young children. Make sure you also have power of attorney documents in place to protect against disability. Execute health care powers of attorney and living wills to provide guidance on difficult choices, should you need serious medical treatment.

These documents cover the basics, but remember, your legacy extends beyond money. Be intentional about passing on your values and your story. Remember, the proverb says, “A good man leaves an inheritance to his children’s children.”

\(^1\) American Bar Association study quoted in FPA Journal of Financial Planning, March 2017
\(^2\) Morris, Hay & Kinghorn, quoted in FPA Journal of Financial Planning, March 2017
Welcome to this issue of South Dakota Medicine, where we have a number of interesting manuscripts for your review.

Chester B. McVay, MD, developed an open surgical technique for repairing an inguinal hernia which has become one standard method of repairing these hernias. In this issue of the journal, Brendan Feehan, a current fourth-year University of South Dakota Sanford School of Medicine (USD SSOM) student, reports on a “laparoscopic pediatric inguinal hernia repair: overview of ‘true herniotomy’ technique and review of current evidence,” which was awarded the 2016 South Dakota Chapter of the American College of Surgeons Chester B. McVay, MD Award. Mr. Feehan matched in anesthesiology at the University of Alabama Medical Center in Birmingham.

In this issue, we continue the pharmacogenomic series expertly arranged by Russell A. Wilke, MD, chair of the Department of Internal Medicine at the USD SSOM. Dr. Wilke has arranged several fascinating articles exploring the effects various genes can have on the effectiveness and side effects of different medications. In this issue, Wenjie Jessie Lu, PhD, and Srekanth Chavour, MD, explore the important area of opioid pharmacogenomics.

Tying in nicely with Lu and Chavours’ manuscript, Timothy Soundy, MD, and co-authors explore the genetics of alcoholism. In this manuscript, the authors discuss the metabolism of alcohol and how genes can affect this metabolism and potentially increase the risk of dependence. They discuss major and minor genetic factors as well as interactions with the environment which may affect the risk of developing dependence on alcohol.

This issue also has a couple of case reports which are enlightening on superior ophthalmic vein thrombosis and tularemia. Superior ophthalmic vein thrombosis is a rare condition with significant morbidity. This article reviews the management of a case of superior ophthalmic vein thrombosis and discusses the controversy surrounding the need for anticoagulation. In the case report of an unusual presentation of tularemia, the authors note that there has been an increase in the number of cases of tularemia and many of them have atypical presentations.

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Earlier this year, *South Dakota Medicine* began publishing a series of monthly articles dedicated to reviewing the pros and cons of gene-based drug dosing. The first article in this series was a point-counterpoint by local content experts exploring the utility of CYP2C19 genotyping for patients taking clopidogrel. We now present the fifth point-counterpoint article in this series—a discussion about CYP2D6 genotyping for patients taking opioids.

**Wenjie Jessie Lu, PhD:** “CYP2D6 genotyping reduces therapeutic failure with opioids”

Pain medications are among the most commonly prescribed medications in the United States. Despite the common use of this important class of drugs, effective pain management is still widely recognized as inadequate in many settings. Prescription drug misuse and risk for overdose are a concern with all pain medications but particularly with the most potent: the opioid class of drugs. Codeine efficacy in particular has wide variability across the general population. This is in part due to the fact that codeine is a prodrug.

The efficacy of codeine is strongly related to the activity of each patient’s liver enzyme CYP2D6. In a person with poor activity of CYP2D6, not enough codeine is converted to active drug and therefore codeine will often not work as well for this person. In a person with very high activity, codeine is converted too rapidly, and that person may be at risk of complications due to overdose. Clinical forms of opioid toxicity include nausea, vomiting, dry mouth, constipation, and respiratory depression. The vast variability in patient response to medications makes it challenging to determine in advance which prescribed medications will actually be effective in any individual.

The trial-and-error approach to opioid prescribing is very costly and it may put patients at risk for undue suffering that results from delays in effective care, inappropriate or unnecessary medication use, and adverse drug reactions. Among the tools available to implement a more personalized approach that has greater precision, pharmacogenetics has emerged as a practical means of determining interindividual differences in the efficacy and toxicity of medications that result from inherited genetic variation in drug-metabolizing enzymes, transporters, receptors, and other drug targets. Genotyping for variation in CYP2D6 holds great promise to reduce therapeutic failure with opioids. The impact of CYP2D6 genotype on several opioid analgesics is explored below.

**Codeine**

Codeine is an opioid with mild to moderate analgesic properties and mild sedative effects. It also acts centrally to suppress cough, and as an antidiarrheal, and is widely used for both. There is substantial evidence linking CYP2D6 genotype to variability in codeine efficacy and toxicity, since the analgesic effects of the drug appear to be primarily mediated by its more potent metabolite, morphine, which is approximately 200 times more potent and whose formation is highly dependent on metabolism by CYP2D6. Individual patients who are poor metabolizers of CYP2D6 may experience markedly less pain relief when codeine is used to treat their pain, whereas severe or life-threatening toxicity can occur after normal doses of codeine have been administered to ultrarapid metabolizers. A large body of literature has contributed to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of pharmacogenetic testing during treatment with codeine. Recent data include a population simulation of 320,000 individuals in which the dominant role of CYP2D6 activity in morphine exposure was reproduced.

Public discussions have focused on the dangers that the ultrarapid CYP2D6 genotype poses to children taking codeine. Codeine-related fatality and severe respiratory depression cases were reported after tonsillectomy in children who were later identified to be rapid metabolizers. As a result, the Food and Drug Administration announced its strongest and new black box warning against codeine use...
to manage postoperative pain in children following tonsillectomy. The codeine product label also informs patients about the increased risk of morphine overdose in breastfed infants whose mothers are taking codeine and are ultrarapid metabolizers. Multiple genes in the pathways of drug absorption, distribution, metabolism, and elimination may impact tissue drug levels. One study found that genetic testing for CYP2D6 and ABCB1 (an ATP cassette binding protein that acts as a tissue specific transporter) predict 81 percent of the cases of codeine-induced CNS depression in breastfed infants and their mothers. When genetic testing was combined with clinical factors, the accuracy rose to 87 percent with a sensitivity of 80 percent and a specificity of 87 percent.\textsuperscript{7}

Tramadol

Tramadol is a narcotic analgesic indicated for the treatment of moderate to severe pain. It is widely used to treat postoperative, dental, cancer, and acute musculoskeletal pain and as an adjuvant to other nonsteroidal anti-inflammatory drugs in patients with osteoarthritis. Like codeine, tramadol is metabolized by CYP2D6 to an active metabolite, (-)-O-desmethyl-tramadol that contributes importantly to its action.\textsuperscript{8} More than a dozen studies have consistently shown a positive association between tramadol pharmacokinetics and CYP2D6 genotype. A total of nine studies in 978 patients documented tramadol-induced changes in either pupillary miosis, efficacy or adverse effects, all associated with CYP2D6 genotype. The data available indicate that patients who carry poor metabolizer genotypes have a four-fold lower response rate to tramadol, and lower adverse effects.\textsuperscript{9} Therefore, a large number of opiate analgesics are available to patients as alternatives to tramadol if CYP2D6 genotype indicates a low chance of response.

Hydrocodone

Hydrocodone is metabolized to hydromorphone by CYP2D6 enzymes, and hydromorphone has a 10- to 33-fold greater affinity for binding to △-opioid receptors than hydrocodone.\textsuperscript{10} Pain relief has been correlated with plasma concentrations of hydromorphone in these patients, and not with hydrocodone.\textsuperscript{11} In a CYP2D6 poor metabolizer, hydrocodone may not be effectively metabolized into hydromorphone, and therefore the patient may have altered analgesic response.

In summary, pharmacogenetic testing may help optimize the choice of effective opioid analgesics while minimizing side effects. The availability of CYP2D6 genotyping makes it clear that there are few practical impediments to obtaining testing: the challenge therefore is how to best use the available tools to improve pain control. As already discussed, CPIC released guidelines on codeine use based on CYP2D6 genotype test results, along with the Canadian Pharmacogenomics Network for Drug Safety.\textsuperscript{5,12} The Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy has also established gene-based therapeutic (dose) recommendations for 53 medications, including codeine, oxycodone, and tramadol.\textsuperscript{13} Organized and consistent pharmacogenetic testing may become more widely adopted in clinical pain management given the recent publication of guidelines on this topic.

Sreekanth Chavour, MD: “Genotype has a limited role in guiding opioid therapy”

As noted by Wenjie Jessie Lu, PhD, gene-based drug selection may enhance our ability to prescribe medications more safely.\textsuperscript{1} However, the utility of this approach varies from one drug class to another.\textsuperscript{2,14} Opioid analgesics are commonly used in routine medical practice, and opioid efficacy is highly variable, making this class of drugs an attractive target for exploring the potential utility of gene-based dosing strategies.

The liver enzyme CYP2D6 helps convert codeine and tramadol to more potent metabolites morphine and O-desmethyltramadol.\textsuperscript{15} The impact of CYP2D6 on other opioids varies drug by drug, with CYP2D6 having little direct effect on hydromorphone and fentanyl.

The idea that, if we know each patient’s “activity level” ahead of time, we can make predictions about opioid selection that will improve pain control and avoid toxicity seems intriguing. While this idea sounds simple, there are many things that need to be considered before we can put this principle to practical use. Several challenges are outlined below.

Issue # 1: Genetic complexity

More than 100 alleles (alleles are variants of enzymes) for CYP2D6 have been identified by genetic testing. Phenotype (how the person actually responds if he/she has these alleles) has not been fully characterized for all these genotypes. Most of the information that we get from assessing and evaluating the genetic tests is predicted by models/theories. Further, there have been no randomized controlled trials to prospectively assess the strength of this relationship.
Issue # 2: Phenotypic diversity
Based on the activity of the CYP2D6 enzyme, people can be classified as “poor metabolizers” (activity level 0), intermediate metabolizers (activity level 0.5), extensive metabolizers (activity level 1-2) and ultra-rapid metabolizers (activity level greater than 2). The percentage of poor metabolizers in the general population is anywhere from 0 to 10 percent and ultra-rapid metabolizers are 0 to 29 percent. Therefore, 60 percent of the general population (intermediate and extensive metabolizers) may not benefit from this testing. Further, activity of cytochrome P 450 enzymes in general can be increased or decreased by other medications that the person might be taking. For instance, if an intrinsic ultra-rapid metabolizer of CYP2D6 (with an activity level of enzyme greater than 2) is taking other medications that inhibit the activity of the enzyme then the enzyme activity score would decrease from greater than 2 to less than 2, depending on the degree of inhibition (strong versus moderate versus weak inhibition of the enzyme) and how many other medications he/she is taking which have similar effect on the enzyme. Thus, there is a dynamic interaction between the genetic blueprint and the phenotype, and this interaction can make it difficult to interpret the genetic information.

Issue # 3: Bioinformatic issues
Unlike some laboratory test results that we routinely order, genetic test results can impact decision making for a patient many years later. These results need to be reported accurately and placed in a person’s chart in a way that facilitates easy access to the information. For most practices, electronic medical records are not yet equipped to facilitate such a process longitudinally. At present, providers would have to dig in the chart to find genetic results and then cross check all of the patient’s medications before they initiate a prescription or facilitate further medication reconciliation. In a health care system where time spent with a provider is at a premium, and waiting lists to see a provider are getting longer and longer, this seems impractical.

Overall, the idea that genetic testing can be used to guide opioid therapy is exciting, but given our limited knowledge about how best to interpret and use these results, many remaining obstacles make gene-based opioid selection and gene-based opioid dosing quite challenging. Given the burgeoning cost of health care, and current lack of clarity about insurance coverage regarding this approach, gene-based opioid selection does not seem like an optimal approach at this point of time. Using pharmacogenetic tests to make routine health care decisions is less appealing for opioids than for some other agents. The old adage “start low and go slow” still seems to be the most economical and the most practical way to prescribe opioids at this time.

REFERENCES


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Introduction

Isolated orbital vein thrombosis is a rare disease that can result in significant morbidity and mortality. Most morbidity and mortality arise due to the involvement of the cavernous sinus. Cavernous sinus thrombosis (CST) can result in significant consequences such as residual cranial nerve weakness and blindness. The role of anticoagulation in the treatment of CST is controversial but appears to reduce morbidity if initiated early. The role of anticoagulation in isolated orbital vein thrombosis is not clear. In this article, we present a case of isolated orbital vein thrombosis and review the evidence for and against anticoagulation.

Case Report

An 88-year-old patient presented to their local hospital with a one-week history of intractable headache, nausea, vomiting, and failure to thrive. The headache was described as a 10/10 in severity and involved the left frontal area. They also noted fevers. They denied any history of cough or sore throat but complained of sinus drainage and left posterior neck and ear pain. The patient was afebrile, but upon examination, it was noticed that the left eye was edematous and erythematos, with matting of the eyelids. There was also injection of the left conjunctiva. Visual acuity was recorded as intact, with pupils equal and reactive to light and accommodation and extraocular muscles displaying the full range of movement. The patient’s neck was supple, with tenderness to palpation over the posterior musculature of the cervical spine. No focal neurological deficits were noted. Laboratory evaluation demonstrated a leukocytosis (15.7 K/uL) with a left shift, and blood cultures were drawn. The comprehensive metabolic panel was normal. A computed tomography scan of the brain showed no signs of a mass, acute bleeding, or stroke. There was, however, evidence of acute on chronic right sphenoid sinusitis. The patient was admitted to the hospital due to hypovolemic shock.

Abstract

Purpose: To report a case of superior ophthalmic vein thrombosis (SOVT) and review the available literature to assess if anticoagulation is warranted in all cases of SOVT.

Observations: The patient presented to an outside hospital facility with a severe headache involving the left frontal temporal area. This progressed to left-sided ptosis and facial droop. Magnetic resonance imaging revealed a left SOVT secondary to sphenoid sinusitis. Treatment was initiated with vancomycin and cefepime, and the patient was transferred to our tertiary care center for further management. Upon arrival at our facility, her symptoms had significantly improved compared to prior documented findings.

Conclusions and Importance: Due to the rarity of SOVT, large clinical studies assessing the necessity of anticoagulation are not likely to be conducted. A review of the literature suggests the use of anticoagulation is determined on a case-by-case basis, taking into account symptom severity. Our case demonstrates that a resolution of symptoms is possible without anticoagulation. The decision to initiate anticoagulation will continue to require a clinician to perform a detailed physical examination to determine if the patient is responding to antibiotic treatment alone.
treatment of sinusitis. Empiric ceftriaxone was initiated for the sinusitis, and tobramycin eye drops were started with warm compresses for the left eye conjunctivitis.

Over the next day, the patient’s headache and leukocytosis resolved. However, the patient developed a left eye ptosis and left facial droop. Magnetic resonance imaging (MRI) was performed and revealed acute on chronic sphenoidal sinusitis, meningitis, and left superior ophthalmic vein thrombosis with extension to the left cavernous sinus (Figure 1). The MRI findings raised questions of a fungal etiology for the sinusitis due to the subtle, bony destruction of the basisphenoid bone. A lumbar puncture was performed but was negative for meningitis. Vancomycin was initiated, and the ceftriaxone was switched to cefepime for Pseudomonas coverage. The patient was then transferred to our facility due to the possibility of cavernous sinus thrombosis and the need for coordinated care from various specialties.

Upon presentation to our hospital, the patient had marked improvement compared to prior documented findings. An ophthalmologic examination showed the patient’s visual acuity was 20/100 in the right eye and 20/30 in the left eye. Pupils were equally round and reactive to light without a relative afferent pupillary defect. Intraocular pressure was 14 in the right eye and 13 in the left eye as measured with Tono-Pen tonometry. Confrontational visual fields were full, and the patient was able to count fingers with both eyes. Extraocular movements in both eyes were full without pain. An external examination revealed normal eyelids and eyelashes. The anterior segment exam of both eyes showed the following: the conjunctivae and sclera were white; the anterior chambers were deep without signs of inflammation; the corneas were clear; and both irises were flat with no evidence of neovascularization. There was the presence of age-appropriate cataracts in both eyes. A funduscopic examination showed a normal optic nerve with a normal cup-to-disc ratio in the right eye and some pallor of the left optic nerve with a normal cup-to-disc ratio. Blood vessels in both eyes appeared normal. In addition to these findings, dry age-related macular degeneration was noted to be greater in the right eye than the left, which likely represents the decreased visual acuity noted above.

Vancomycin and cefepime were continued, and metronidazole was added for anaerobic coverage. The patient continued to improve dramatically, and this was attributed to the empiric antibiotic therapy. MRI results were reviewed again, and this confirmed the findings of thrombosis of the left superior ophthalmic vein, but the findings of left cavernous sinus thrombosis were equivocal. Therefore, with the patient’s dramatic improvement in clinical status, combined with imaging being not definitive for the diagnosis of cavernous sinus thrombosis, anticoagulation was held.

A bilateral sphenoidectomy with cultures was performed to rule out a fungal etiology. The bilateral nares cultures grew Penicillium species. An infection with this species is usually opportunistic and only impacts people infected with human immunodeficiency virus (HIV). Because our patient tested negative for HIV and improved significantly with therapy, the antifungal treatment was not added. An

Figure 1. T1 and T2 axial images showing hypointensity and dilatation (arrow) involving the left superior ophthalmic vein (A and B). T1 coronal fat suppressed with contrast image showing filling defect (arrow) of the left superior ophthalmic vein (C).
aerobic culture from the left nares did have light growth of *Corynbiacterium jeikeium*, which tends to cause opportunistic infections in bone marrow transplant patients. However, no adjustment of therapy was required since it was susceptible to vancomycin. All blood cultures were negative.

The patient had complete resolution of the left eye edema and erythema. The left eye vision remained stable at 20/30. They were discharged to a long-term care facility with plans to continue treatment with vancomycin, cefepime, and metronidazole for a total of six weeks.

**Discussion**

Treatment of superior ophthalmic vein thrombosis (SOVT) is guided by physician experience and judgment, as large-scale studies have not been done and are not forthcoming due to the condition’s rarity. In the case of SOVT secondary to infection, the rationale for anticoagulation is clear and involves clot stabilization and canalization of the thrombus, facilitating the penetration of antibiotics into the infected clot. It is also surmised that anticoagulation may prevent extension to CST. However, due to the rarity of SOVT, use of anticoagulation is still debated because though it may prevent extension to CST, there is the possibility of it causing septic emboli or hemorrhage. If treatment recommendations for CST can be extrapolated for SOVT, then it is reasonable to base the use of anticoagulation on a patient’s response to initial medical management. If the patient is improving and not showing decreases in visual acuity, proptosis, focal neurological deficits, or other signs of extension into the cavernous sinus, anticoagulation can be held. However, if the patient is not responding to therapy and having increased deficits attributable to SOVT, it may be reasonable to initiate anticoagulation after a risk-benefit analysis has been reviewed with the patient. If there are no contraindications to anticoagulation and the clinical setting suggests that further intervention is needed, it should be initiated within seven days of diagnosis. Early anticoagulation combined with antibiotics compared to late anticoagulation with antibiotics appears to be more effective in decreasing morbidity. In conclusion, the decision of whether or not to anticoagulate patients with SOVT will continue to be based on a patient’s clinical course and the physicians’ experience and judgment due to the lack of evidence-based approaches.

Acknowledgements: We thank Catherine Hensley for editing assistance.
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A PUBLIC HEALTH MESSAGE FROM THE SOUTH DAKOTA DEPARTMENT OF HEALTH
Atypical Presentations of Tularemia

By Karah Odegaard, MSIV; Kirstin Hockhausen, MSIV; Beth Boersma, LPN, CIC; and James M. Keegan, MD

Abstract

Francisella tularensis is a gram-negative coccobacillus that causes a condition commonly referred to as tularemia. There has been a dramatic increase in tularemia cases reported in South Dakota, many of which were challenging to diagnose due to atypical clinical manifestations. We describe an interesting case of pneumonic tularemia and summarize six similar cases, several of which presented with lung nodules suggestive of malignancy. According to the literature, this is only the third outbreak of pneumonic tularemia reported in the U.S. We believe it is important for clinicians to be aware of the increased incidence of tularemia in the area and to be vigilant in the diagnosis and management of these atypically presenting cases.

Introduction

Francisella tularensis is a gram-negative coccobacillus that causes a condition commonly referred to as tularemia. Although tularemia is seen throughout the world, it is most prevalent in the Northern Hemisphere. Flea and tick bites and exposure to rabbits, cats, rodents or contaminated animal products are common modes of transmission. The majority of tularemia cases in the U.S. occur in Arkansas, Kansas, South Dakota, Missouri, Nebraska, and Oklahoma. There has been a dramatic increase in tularemia cases reported in South Dakota, shifting from an average of seven cases per year over the last five years to a reported 25 cases in 2015. There has not been an outbreak like this in South Dakota since 1984, when Lower Brule and Crow Creek Indian reservations endured an outbreak of tick-borne tularemia.

Tularemia classically presents with a sudden onset of fever, chills, headache, malaise, anorexia, and fatigue, and is often accompanied by cough, myalgia, chest discomfort, vomiting, sore throat, abdominal pain, and diarrhea. Patients with tularemia typically have a fever greater than 101 degrees Fahrenheit that lasts for several days. The fever often diminishes for a short time and later returns as the disease progresses. There are several presentations of tularemia, the most common being ulceroglandular tularemia. This is the most easily recognized form as it initially presents with localized, tender lymphadenopathy and a red, painful papule that develops into a tender ulcer with a raised border.

Another presentation of tularemia, pneumonic tularemia, is only seen in 7 to 20 percent of cases and is characterized by fever, cough, minimal sputum production, pleuritic chest pain and pulmonary infection. Of the eight cases treated at Rapid City Regional Hospital, seven of the patients presented with pneumonic tularemia. Atypical clinical manifestations made these cases difficult to diagnose, thereby making treatment decisions more challenging. It is important that clinicians be aware of the increasing prevalence of this disease and recognize the possibility of tularemia in patients with abnormal respiratory findings.

Case Report

A 58-year-old Caucasian male with a previous history of squamous cell carcinoma of the vocal cords presented to an emergency department in Wyoming with symptoms of generalized ache, malaise, cough with production of grey-brown sputum, and fever with sweating and chills. He also complained of new onset pleuritic chest pain. He was prescribed amoxicillin-clavulanate, but showed no improvement in symptoms over the following five days. The patient recalled recent exposure to many old, deceased rabbits while working in a field and also...
sustained multiple insect bites during this time.

On the sixth day of symptoms, the patient was transferred to Rapid City Regional Hospital. At this time, he was found to have a temperature of 37 degrees Celsius, pulse of 77 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 126/72 mmHg, and pulse oximetry of 94 percent. Physical exam revealed occasional respiratory crackles and an absence of adenopathy. His laboratory studies showed a leukocyte count of 10,100/mL (4,500-10,500/mL) and a normal white cell count differential. The patient was also noted to have abnormal liver function tests, including aspartate aminotransferase level 112 IU/L (normal range of 0-37 IU/L), alanine aminotransferase 198 IU/L (normal range of <78 IU/L), and alkaline phosphatase 258 IU/L (normal range of 55-142 IU/L). The patient was also nonreactive to hepatitis B surface antigen, hepatitis B core antibody and hepatitis C antibody.

The chest radiograph on initial presentation in Wyoming was negative. However, a computed tomography angiography of the chest obtained to rule out a pulmonary embolism revealed a spiculated, 2.5 x 2 cm nodule and a smaller, nonspecific density, both located in the left lower lobe with hilar lymphadenopathy. These findings were suspicious for malignancy. A CT-guided biopsy was performed. Histology from the larger nodule showed inflammation, necrosis, fibrin without granulomatous tissue, and reactive pneumocytes. Special staining did not reveal fungi or acid-fast organisms. Blood cultures were negative, however lung tissue grew gram-negative coccobacilli. The patient was started on antibiotic therapy with intravenous gentamicin and ceftriaxone. The culture was sent to the South Dakota Department of Health and confirmed as Francisella tularensis. On the sixth day of the gentamicin therapy, the patient felt his breathing had improved and the pleuritic chest pain relieved. He was discharged with a plan to finish a 10-day course of gentamicin, followed by a two-week course of oral ciprofloxacin.

As previously stated, there were multiple cases of pneumonic tularemia treated at Rapid City Regional Hospital in 2015, which were similar to the case presented. All cases, including the case report (Case 1), are summarized in Table 1. Most of these cases presented with the classic findings of pneumonic tularemia including fever, cough, and pleuritic chest pain. They also had the classic radiographic findings of pleural effusions, subsegmental or lobar infiltrates and hilar lymphadenopathy. However, as seen in Table 1, five patients also presented with pulmonary masses or nodules, which raised suspicion for malignancy as opposed to an infectious process. Diagnosis was made in all cases either by pleural fluid culture, lung tissue biopsy and culture, or blood cultures. Upon diagnosis, patients were treated with either single or combination antibiotic therapy with ciprofloxacin, gentamicin, or doxycycline and all had positive outcomes.

For all cases of pneumonic tularemia, patient exposure history was obtained and is reviewed in Table 2.
All seven of the pneumonic cases were treated as either community-acquired or hospital-acquired pneumonias, but did not respond to common antimicrobials such as ceftriaxone, vancomycin, azithromycin, piperacillin-tazobactam, ampicillin-sulbactam, ceftazadime, and nafcillin. Because patients did not respond to the typical treatments of pneumonia, they were started on less common empiric therapies including acyclovir, amoxicillin-clavulanate, and metronidazole. Three of the seven patients were also considered immunocompromised at the time of presentation, which may have also influenced their initial treatment. Each patient was placed on at least one antimicrobial prior to their diagnosis of tularemia, with an average of 3.75 antimicrobials used before initiating tularemia-specific therapy. This ultimately delayed targeted treatment as these patients spent time in the hospital on other antimicrobials prior to starting either individual or combination therapy with gentamicin, ciprofloxacin, or doxycycline, the recommended antibiotics for tularemia. All patients had good outcomes, as they received appropriate treatment. However, in the pre-antibiotic era, the mortality rate was as high as 60 percent, compared to the current national mortality rate of less than 2 percent.6,7 Due to the difficulty of diagnosis of this condition, there were likely more cases of tularemia not identified. Early clinical suspicion is critical, especially for the protection of our laboratory workers who have a high risk of tularemia exposure from processing of laboratory specimens. Therefore, we believe that awareness to these atypical presentations and the increasing incidence of pneumonic tularemia in South Dakota is important for clinicians to consider in order to avoid delayed diagnosis and treatment.

Classically, pneumonic tularemia presents with pleural effusions, subsegmental or lobar infiltrates, and hilar lymphadenopathy.1 Though six cases did present with these particular findings, there were four cases that also revealed lung nodules or masses and one case that presented with only a pulmonary nodule, all of which were concerning for the possibility of malignancy (see Table 1). One of these cases had a 15-mm nodule in the left upper lobe with no other pulmonary findings. Lung biopsies were performed on four of the cases that presented with lung nodules or masses to rule out malignancy. Culturing of these biopsies led to the positive diagnosis of *F. tularensis* in three of the four cases. Three cases were identified as tularemia via pleural fluid culture confirmed by direct fluorescence antibody testing and one case was found to have a positive blood culture.

**Table 2. Comparison of Known Patient Exposures**

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Number of Patients Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits</td>
<td>2</td>
</tr>
<tr>
<td>Rodents</td>
<td>1</td>
</tr>
<tr>
<td>Cats</td>
<td>4</td>
</tr>
<tr>
<td>Lawn-mowing</td>
<td>3</td>
</tr>
<tr>
<td>Insect bites</td>
<td>2</td>
</tr>
</tbody>
</table>

## Discussion

According to the literature, this is only the third outbreak of pneumonic tularemia reported in the U.S., with the previous outbreaks both occurring in Massachusetts on Martha’s Vineyard in the years 1978 and 2000.1 Though South Dakota did have an outbreak in 1984 with 20 definite and eight probable cases reported, the clinical presentation suggested a glandular type of tularemia, with ticks as the primary vector.1 Of the eight cases seen in 2015, seven have been characterized as the pneumonic type. Though two cases had sustained insect bites, none specified any history of tick exposure. However, four cases reported prior exposure to cats, two to rabbits, and one to rodents, as seen in Table 2. Three patients also stated that they mow their own lawns. The outbreak of primary pneumonic tularemia in Martha’s Vineyard revealed common exposures of lawn-mowing and brush-cutting as risk factors for development of the infection.5 Without significant evidence supporting vector transmission in these cases of pneumonic tularemia, this raises the question of possible transmission through a respiratory route and suggests that aerosolization of the bacteria could be a potential risk factor in the environment, though person-to-person transmission is not well-documented.1,7

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Pre-Guideline Trends Associated with Chest Radiograph Usage for Pediatric Community-Acquired Pneumonia in Emergency Department Settings

By Eric W. Jones, MSIV; Benjamin Meyer, MD; Aaron M. Berg, MD; Benson S. Hsu, MD, MBA

Abstract

Background: Health care spending in the U.S. totaled $3 trillion in 2014 and continues to increase rapidly. Minimizing waste through clinical guidelines is a promising strategy to reduce spending without compromising patient care. In 2011, clinical guidelines recommended against the use of chest X-ray (CXR) for diagnosis of community-acquired pneumonia (CAP) in pediatric ambulatory settings. However, use of CXR has not changed post-guideline. Thus, understanding the drivers of CXR utilization prior to guideline implementation could improve guideline adherence.

Methods: Retrospective study using 2009 Nationwide Emergency Department Sample data set consisting of a representative sample of all emergency room admissions. Inclusion criteria consisted of: 18 years of age or younger and the diagnosis of outpatient CAP. Population was segmented by the presence of a CXR obtained during the visit. Socioeconomic status was determined by quartile classification of the estimated median household income based on patient ZIP code.

Results: In 2009, children living in wealthier ZIP codes presenting to the emergency department (ED) who were diagnosed with CAP were more likely to receive diagnostic CXR. The use of chest radiograph was not statistically correlated to gender, weekday versus weekend admission, number of diagnoses at discharge, or total ED charges.

Conclusion: The research demonstrates a strong correlation between socioeconomic status of the pediatric patient and use of chest radiograph for CAP in the ED setting prior to 2011 guideline publication. Further research to determine the reason for this correlation could give rise to focused efforts to successfully encourage adherence to clinical practice guidelines.

Introduction

U.S. health care costs totaled $3 trillion in 2014, accounting for 17.5 percent of the overall U.S. economy. Reducing health care cost is essential for long-term sustainability. It has been estimated that 30 percent of health care spending in 2009 was wasted on unnecessary medical services. Decreasing unnecessary services reduces spending without compromising patient care.

Pneumonia is a leading cause of hospitalization in children, and currently available diagnostic studies are relatively insensitive. Specifically, chest radiograph has been shown not to improve clinical outcome in an ambulatory setting, yet approximately $189-496 million each year is spent on chest X-ray (CXR) for diagnosis of community-acquired pneumonia (CAP) in an outpatient setting. Moreover, substantial disagreement exists in the interpretation of CXR to diagnose CAP, suggesting that it is an unreliable diagnostic tool.

Given the cost of CXR and inconsistency of evidence to demonstrate improved outcomes, the use of CXR is a promising area for the application of clinical guidelines aimed to encourage consistency and reduce unnecessary cost. In 2011, the Infectious Disease Society of America
(IDSA) along with the Pediatric Infectious Disease Society (PIDS) published guidelines for the management of CAP for infants and children older than 3 months of age. According to guidelines, CXR is not necessary to confirm CAP in an ambulatory child who is otherwise healthy. Instead, CXR is recommended for patients with hypoxemia, significant respiratory distress, or after failed antibiotic treatment to confirm the presence or absence of complications such as parapneumonic effusions, necrotizing pneumonia, or pneumothorax.

Despite consensus among experts on best practice, implementation of these guidelines was not successful in changing physician behavior. Before guideline implementation, no studies were published to determine groups of children who receive CXR most often. Given the difficulty of producing clinical guidelines effective in changing physician behavior, more information on pre-publication trends and patterns of behavior would provide useful insight to tailor implementation plans. While these patterns may not describe reasons why emergency department (ED) physicians make decisions, they can provide useful insight into how to better encourage adherence to the published guidelines. The purpose of this study is to examine pre-publication trends in physician practice in the setting of pediatric outpatient pneumonia in order to identify patterns correlated with non-adherence to clinical guidelines with the hope that this knowledge may provide insight and direction into successfully encouraging adoption of clinical guidelines.

Methods

Study Design and Data Source

We performed a retrospective study of hospitalized children utilizing the 2009 Nationwide Emergency Department Sample (NEDS), a part of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality (AHRQ). This data set is available every three years with the 2009 sample being the most recent data set available prior to the implementation of the new IDSA/PIDS consensus guideline on the management of pediatric CAP.

Due to the de-identified nature of the patient data, the project received exempt status from the institutional review boards of Sanford Health and University of South Dakota Sanford School of Medicine.

Case Definitions

Patients 18 years or younger with CAP were identified through the use of a previously validated International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) algorithm. Patients were identified with CAP if they had a primary ICD-9-CM diagnosis of pneumonia (480-483 and 485-486) or a primary diagnosis of a pneumonia-related symptom such as fever or cough (780.6, 786.0, 786.2-5, 786.7) and a secondary ICD-9-CM diagnosis of pneumonia, empyema (510), or pleurisy (511.0-1 and 511.9). Outpatient status was based on discharge from facility following treatment. All outpatient status was based on discharge from facility following treatment. All outpatients 18 years or younger with a diagnosis of CAP in the emergency setting identified by this algorithm met the inclusion criteria. All others were excluded.

Socioeconomic status was determined by a quartile classification of the estimated median household income of residents in the patient's ZIP code as provided by AHRQ. In 2009, the quartile ranges were: $1-$39,999, $40,000-$49,999, $50,000-$65,999, and $66,000+.

Statistical Analysis

All statistical analyses were conducted using STATA/IC 12.1 (StatCorp, College Station, Texas). Given the complex sampling of survey data present in KID, we utilized the weighted analysis function (“svy” command) in STATA/IC to determine the mean and 95 percent confidence intervals. Tests to compare the mean values were performed using the adjusted Wald test. All values presented are based on weighted analysis. Statistical significance was established at p value <0.05.

Results

There were 99,814 observations in the sample population meeting the criteria of CAP within NEDS. These observations represented an overall population of 445,078. Overall demographics showed that 45 percent of the population received CXR while 55 percent of the population did not. There was little difference noted in age or gender. Clinically, the two populations did not differ in the number of diagnoses at discharge, and total ED charges.

From a view of charges, total charges were higher for those who did not receive a CXR at $1,516 (95 percent confidence interval of $1,500 to $1,532) versus those who received a CXR at $1,498 (95 percent confidence interval
of $1,486 to $1,510). This was not statistically significant with the p value being 0.08.

In respect to socioeconomic status, pediatric patients living in ZIP codes with the lowest estimated median household income quartile were the least likely to receive CXR for a diagnosis of community-acquired pneumonia while pediatric patients living in ZIP codes with the highest estimated median household income quartile were the most likely to receive CXR for a diagnosis of CAP (Figure 1).

**Discussion**

In 2009, children living in wealthier ZIP codes presenting to the ED who were diagnosed with CAP and discharged home were more likely to receive diagnostic CXR than their less wealthy peers. The use of chest radiograph did not correlate with statistically different total ED charges, gender, weekday versus weekend, or number of diagnoses at discharge.

Health care costs are currently a major concern in the U.S., and minimizing waste is a promising strategy to reduce spending without compromising patient care. Clinical guidelines which achieve this purpose in the setting pediatric CAP were published in 2011. These guidelines discourage the use of CXR for diagnosis of CAP in ambulatory children on the basis that CXR has been shown not to improve patient outcome and has been shown to be an unreliable diagnostic tool. Eliminating CXR usage for children who are treated outpatient for CAP could potentially save hundreds of millions of dollars each year in the U.S.

Despite expert guidelines discouraging use of CXR for diagnosis of CAP in an ambulatory patient, studies have not shown a resultant change in physician practice. A recently published study examined pediatric patients with a diagnosis of CAP who were discharged from the ED in a sample of children’s hospitals. This study demonstrated that the rate of CXR usage over the years 2008 to 2014, three years before and three years after publication, remained unchanged. Similarly, use of other unnecessary diagnostic testing such as blood culture, CBC, CRP changed minimally, resulting in only modest cost reduction. Researchers noted wide variations in diagnostic testing between hospitals before and after guideline publication. Similarly, the Etiology of Pneumonia in the Community (EPIC) study reported significant variation in diagnostic testing between hospitals, and that hospitalist diagnosis of CAP differed from ED physician for 47 percent of admissions.

The lack of adoption of guidelines is not specific to CAP. The 2004 guidelines for the management of acute otitis media (AOM) allow for watchful waiting instead of immediate antibiotic treatment in certain cases. This guideline was based on evidence that resolution of AOM often occurs with or without antibiotic treatment and that

<table>
<thead>
<tr>
<th>Table 1. Demographics of Sample Population (n = 444,705)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
</tr>
<tr>
<td>(95% Confidence Interval)</td>
</tr>
<tr>
<td>Received CXR</td>
</tr>
<tr>
<td>4.3 (4.27 – 4.35)</td>
</tr>
<tr>
<td>Did Not Receive CXR</td>
</tr>
<tr>
<td>4.37 (4.33-4.41)</td>
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<tr>
<td>p value</td>
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<tr>
<td>0.05</td>
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<tr>
<td>Gender (% Female)</td>
</tr>
<tr>
<td>44.7% (44.3% - 45.2%)</td>
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<tr>
<td>44.9% (44.4% - 45.3%)</td>
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<tr>
<td>p value</td>
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<tr>
<td>0.71</td>
</tr>
<tr>
<td>Diagnosis at Discharge (#)</td>
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<td>2.07 (2.06 – 2.09)</td>
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<tr>
<td>2.07 (2.06 – 2.09)</td>
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<tr>
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<tr>
<td>0.84</td>
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<tr>
<td>Weekend ED Visit (%)</td>
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<td>32.7% (32.3% - 33.2%)</td>
</tr>
<tr>
<td>p value</td>
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<td>0.57</td>
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</table>
watchful waiting does not increase the incidence of serious sequelae. Practicing according to these guidelines reduces spending on antibiotics, decreases the chance of adverse side effects from antibiotics, and prevents antibiotic resistance. Despite these virtues, this recommendation did not result in an increase of management of AOM without antibiotics. Interestingly, a 2012 study showed that neither ethnicity, race, nor insurance status significantly influenced antibiotic prescribing practices of doctors. Socioeconomic status was not analyzed.

With strong evidence to support guideline recommendations, it can be puzzling why guidelines often are not successful in changing physician practice. Reasons behind non-adherence to guidelines have been explored in the literature, with exploration mostly focusing on institutional organizations and physician perceptions. A 2016 study exploring reasons preventing doctors from switching antibiotics from IV to oral found that the three main factors were consumerism (i.e., fear of litigation or dissatisfying patients), hierarchy of medical team, and perception that IV antibiotics were more potent. A study in Saudi Arabia found that organizational barriers and lack of implementation strategy led to doctor non-compliance to pediatric asthma guidelines.

Our study, in pointing out the correlation between socioeconomic status and physician practice patterns, supports prior research that consumerism and organizational barriers may impact non-adherence to guidelines. It might be reasonable to assume that a child from lower socioeconomic status is more likely to receive chest radiograph because ED physicians assign a likelihood of proper follow-up (due to possible financial, transportation, or time constraints) in making the decision for a CXR. However, our data show that in 2009 the opposite was true. The exact reason for this difference is unclear through our research, but consumerism and organization barriers offer a possible explanation.

Consumerism may drive doctors to order other testing, thus explaining why total ED charges were not statistically different between those patients who received CXR and those who did not. Doctors may also be hesitant to do too little for fear of dissatisfying the patient’s parents. Finally, fear of litigation as a basis of our health care system that led to disparity in use of CXR between children living in wealthier ZIP codes. Lastly, this study focused on patient characteristics, and did not delve into physician or hospital characteristics that may be correlated with use of CXR in the ambulatory patient with suspected CAP.

Limitations of this study include that the sample consisted only of U.S. children from a single year, the sample was not broken down further by child's race or geographic area, and socioeconomic status of the child was deduced by ZIP code instead of actual family income (although this practice is well-established in public health literature). Furthermore, this study was not able to identify exact reasons driving provider decisions to order chest radiograph for children living in wealthier ZIP codes. Lastly, this study focused on patient characteristics, and did not delve into physician or hospital characteristics that may be correlated with use of CXR in the ambulatory patient with suspected CAP.

Strengths of the study include a large sample size and a very strong correlation (p<0.001) of CXR use in CAP with children living in wealthy ZIP codes. Six separate variables including age, gender, weekend versus weekday, number of diagnoses at discharge, total ED charges, and median household income based on median household income quartiles for ZIP code were examined for correlation. Most importantly, this study explores the novel idea that examining trends in physician practice prior to guideline publication may lead to improved implementation and that patient characteristics may influence physician adherence to clinical guidelines.

Future studies should seek to determine if there are financial, demographic, or racial biases in the health care system that led to disparity in use of CXR between children living in wealthier neighborhoods. By identifying reasons driving physician adherence to clinical guidelines such as socioeconomic status, targeted interventions can be developed focused on improving guideline implementation acceptance.

Conclusion

Understanding underlying patterns of physician practice prior to guideline release would likely aid in successfully implementing guidelines. Somewhat unexpectedly, this paper demonstrates a strong correlation between socioeconomic status of the pediatric patient and use of chest radiograph for CAP prior to guideline publication in 2011 which discourages ordering CXR in the outpatient setting. Further research is needed to determine the exact reason...
motivating providers to order CXR for children residing in wealthier ZIP codes and to determine what other factors may be associated with non-adherence to guidelines. With this knowledge, focused efforts addressing specific patterns of behavior could be undertaken to more successfully encourage adherence to clinical practice guidelines.

REFERENCES


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Laparoscopic Pediatric Inguinal Hernia Repair: Overview of “True Herniotomy” Technique and Review of Current Evidence

By Brendan P. Feehan, MSIV; and David S. Fromm, MD

Abstract
Inguinal hernia repair is one of the most commonly performed operations in the pediatric population. While the majority of pediatric surgeons routinely use laparoscopy in their practices, a relatively small number prefer a laparoscopic inguinal hernia repair over the traditional open repair. This article provides an overview of the three port laparoscopic technique for inguinal hernia repair, as well as a review of the current evidence with respect to visualization and identification of hernias, recurrence rates, operative times, complication rates, postoperative pain, and cosmesis. The laparoscopic repair presents a viable alternative to open repair and offers a number of benefits over the traditional approach. These include superior visualization of the relevant anatomy, ability to assess and repair a contralateral hernia, lower rates of metachronous hernia, shorter operative times in bilateral hernia, and the potential for lower complication rates and improved cosmesis. This is accomplished without increasing recurrence rates or postoperative pain. Further research comparing the different approaches, including standardization of techniques and large randomized controlled trials, will be needed to definitively determine which is superior.

Introduction
Inguinal hernia repair remains one of the most commonly performed procedures in the pediatric population.¹ It is estimated that inguinal hernia occurs in 1 to 5 percent of all newborns and in 9 to 11 percent of premature newborns.² Boys experience an incidence three to four times higher than in girls.³ The incidence is highest during the first year of life, with peak incidence occurring in the first month.³ Despite the rise of laparoscopy and minimally invasive surgical techniques in the realms of general and pediatric surgery over the last 20 years, many pediatric surgeons remain reluctant to employ laparoscopy in the repair of inguinal hernias. In a recent survey of 187 pediatric surgeons in 46 different countries, 79 percent (148 out of 187) of respondents routinely employed laparoscopy in their practice.¹ However, only 17 percent (32 out of 187) of respondents preferred laparoscopy in the repair of inguinal hernia. Concerns cited by these surgeons include less risk of recurrence, less abdominal organ injury, less vas/vessel injury, and faster operative times with the traditional open approach. Of the 17 percent of respondents that preferred laparoscopy, stated benefits of the technique included less metachronous contralateral hernias, better cosmesis, easier technique, less vas/vessel injury, and less postoperative pain. Proficiency with the technique can be achieved in 10 to 25 procedures, according to 80 percent of the polled surgeons. Despite this reluctance to employ a laparoscopic repair, a review of current literature on the technique does find several advantages, including superior visualization of the relevant anatomy, ability to assess the contralateral inguinal ring and repair a contralateral hernia if present, lower rates of metachronous hernia, shorter operative times, low complication rates, and excellent cosmesis. This article provides an overview of the three-
port “true herniotomy” laparoscopic technique for repair of pediatric inguinal hernias as well as a review of the current evidence on the laparoscopic approach with comparison to the standard open technique.

Overview of Technique

The procedure is set up with the patient supine on the operating table. The table is positioned in a manner that the surgeon stands at the head of the table. Patient is prepped and draped in the usual manner. After administration of local anesthetic, a small stab incision is made along the superior rim of the umbilicus. Veress needle is inserted and the abdomen is inflated with maximum pressure of 6-10 mmHg. The Veress needle is removed and a 5 mm port is positioned through the opening. A 5 mm 30 degree laparoscope is used for visualization while two additional 3 mm ports are placed along the left and right anterior axillar lines slightly cephalad with a horizontal axis of the umbilicus.

The laparoscope is used to identify and assess the hernia (Figure 1). Contents such as omentum or bowel are reduced if needed. The peritoneum lateral to the internal inguinal ring is grasped and incised with laparoscopic scissors. The peritoneum is then mobilized in a circumferential fashion at the internal ring (Figure 2). The laparoscopic view provides excellent magnified visualization of the relevant anatomy, especially the vas deferens, testicular artery, and testicular vein. These structures are identified and protected throughout the procedure. The hernia sac is reduced using gentle hand-over-hand dissection from the spermatic cord. The posterior aspect of the hernia sac is mobilized using sharp scissor dissection from the vas deferens as well as the testicular artery and vein. The hernia sac is retrieved through the 3 mm ports and submitted for pathology review. 4-0 nonabsorbable braided suture is introduced and used to close the internal ring in a multiple figure-of-eight fashion (Figure 3). This is consistent with high ligation of the hernia sac. The process is repeated on the opposite side if bilateral hernia is present.

Following completion of the repair, the laparoscopic ports are removed and the pneumoperitoneum is evacuated. The fascia at the umbilicus is closed with 3-0 absorbable synthetic braided suture in an inverted interrupted fashion. 5-0 monofilament synthetic absorbable suture is used in a running subcuticular fashion to approximate skin edges. Dermabond solution is used to reinforce the skin closure.
Evidence for the Laparoscopic Approach

Superior Visualization and Evaluation of Contralateral Inguinal Ring

One of the biggest advantages to the laparoscopic technique is the superior visualization of the relevant anatomy. The internal inguinal ring is presented in a close-up, magnified view from inside the abdomen that is indisputably superior to the visualization provided by the classic open technique. This allows the surgeon to identify hernias that are not clinically apparent.

Schier's described 129 pediatric patients with 153 inguinal hernias that were pre-operatively diagnosed. Of these, 15 percent (19 out of 129) of patients had an unexpected contralateral internal ring open on the left, while 22 percent (28 out of 129) of patients had an unexpected contralateral internal ring open on the right. Additionally, Schier found multiple instances of clinically diagnosed hernia that were in contradiction with what was visualized with the laparoscope. In the largest series of its kind, Valusek et al. studied 1,676 patients clinically diagnosed with unilateral inguinal hernia by performing laparoscopy to evaluate the contralateral side. Before laparoscopic visualization was performed, patients were examined under general anesthesia by an attending pediatric surgeon. Following these exams, it was predicted that 28 percent (470) of these patients would have a contralateral patent processus vaginalis (PPV). After laparoscopic exam, 40 percent (670) of the patients had a contralateral PPV. In patients that did not have a contralateral PPV on exam, 39 percent did in fact have a contralateral PPV after laparoscopic visualization. An additional study by Mollen and Kane has noted that visualizing the anatomy through a laparoscope at the transumbilical position is superior to clinical exam or extension of pneumoperitoneum into the scrotum.

Additionally, discovery of bilateral hernia is easily remedied with the laparoscopic technique, as the contralateral internal ring can be closed without additional incisions or access. The evidence for routinely closing open internal rings in the absence of clinical symptoms of hernia is controversial. However, metachronous hernia rates are lower when any open inguinal ring that is discovered is routinely closed, according to Schier. In fact, the laparoscopic approach has a lower rate of metachronous hernia, likely due to its ability to easily identify and close an open internal ring. The ability of the laparoscopic approach to discover an undiagnosed hernia and subsequently close it provides a benefit not seen with the conventional open technique.

Recurrence Rates

An important measure for success in inguinal hernia repair is the rate of recurrence. Laparoscopic technique has been criticized as an inferior procedure due to increased inguinal hernia recurrence. Direct comparison of recurrence rates in laparoscopic pediatric inguinal hernia repair is difficult due to variation in techniques. Additionally, defining recurrence is often difficult and varies between surgeons and studies. Schier suggests that pediatric hernias and their recurrences exist on a spectrum, ranging from a partially open internal inguinal ring to “all-the-way-down-into-the scrotum open processes.” However, when comparing the laparoscopic approaches to the conventional open technique in the pediatric population, the available evidence suggests that there is no significant difference in recurrence rates between procedures.

Yang et al. conducted a meta analysis of three randomized controlled trials and four observational clinical studies comparing 1,543 laparoscopic repairs to 657 open repairs. The authors reported that inguinal hernia recurrence rate between the two procedure techniques was not significantly different. An additional randomized controlled trial by Shalaby et al. involving 125 patients undergoing laparoscopic repair and 125 patients undergoing open repair found an inguinal hernia recurrence rate of 0.8 percent (one out of 125) in the laparoscopic group compared to 2.4 percent (three out of 125) in the open group over a mean follow-up period of 24 months. No statistically significant difference was noted. Philippe et al. conducted a retrospective series involving 385 patients with 525 hernia repairs that had four indirect hernia recurrences (0.76 percent of repairs); three at one month post-operatively and one at two years post-operatively. A prospective review by Dutta et al. of 275 laparoscopic hernia repairs in 187 children found a recurrence rate of 1.5 percent (four out of 275) with two or more years of follow-up. A retrospective study involving 884 children documented an inguinal hernia recurrence in 28 children, at a rate of 3.2 percent. In a prospective series involving 712 laparoscopic inguinal hernia repairs in 542 children aged 4 days to 14 years, Schier reported a slightly higher inguinal hernia recurrence rate of 4.1 percent (29 out of 712 repairs) with median follow-up of 39 months. However, this recurrence rate was reported to decrease as experience with the
technique was gained. In a large multicenter study, Schier, Montupet, and Esposito performed 933 repairs in 666 children age 3 weeks to 14 years (median 3.2 years). The reported inguinal hernia recurrence rate was 3.4 percent (32 out of 933 repairs) with follow-up time ranging from two months to seven years. In an additional large multicenter study in Japan, Takehara et al. performed 972 laparoscopic inguinal hernia repairs in 711 children age 18 days to 19 years. The reported recurrence rate with five months to 10 years of follow-up was 0.73 percent (seven out of 972 repairs). A retrospective analysis conducted by Saka et al. reported 326 laparoscopic repairs and 162 open repairs with no significant difference noted in recurrence rates. Parelkar et al. in another retrospective analysis of laparoscopic repair of 437 children undergoing 576 laparoscopic inguinal hernia repairs described a recurrence rate of 2.4 percent (14 out of 576). The published recurrence rates in open inguinal hernia repair range from 0 to 4.7 percent. The published recurrence rates for laparoscopic repair do not vary significantly from those for open repair. However, a direct comparison of recurrence rates between the two approaches is difficult. There are a variety of techniques currently employed in laparoscopic repair, and each technique is updated and changed as surgeons gain experience with them. The adoption of a standard technique for laparoscopic repair would allow for a more direct comparison to the open repair.

Operative Times
An additional concern limiting the adoption of laparoscopic repair is longer operative times. Current evidence suggests that the operative time for laparoscopic repair is no different for unilateral hernia, and possibly superior in bilateral hernia. Shalaby et al. reported that laparoscopic repair was significantly shorter in children with a unilateral hernia (p<0.001) and in children with a bilateral hernia (p<0.001). Philippe et al. note mean operation times of 26.2 minutes for unilateral laparoscopic inguinal hernia repair and 34.5 minutes for bilateral laparoscopic hernia repair. Schier documents a median operating time of 22 minutes with laparoscopic repair. Mean operating time in a retrospective review of 437 children undergoing laparoscopic repair was 23 minutes for unilateral hernia and 29 minutes for bilateral hernia. The meta-analysis conducted by Yang et al. notes no significant difference in operating times between procedures for unilateral hernia; however, there was a significantly shorter operating time (p=0.02) in laparoscopic bilateral hernia repair. Another randomized controlled trial by Celebi et al. compared a laparoscopic procedure to open repair in bilateral hernias of 62 boys ranging in age from 6 to 14 years. The authors found the operative time for laparoscopic repair to be slightly shorter, although the difference was not statistically significant. The limiting factor for operative times in laparoscopic repair is generally the familiarity and skill with laparoscopy of the surgeon, and operating times tend to decrease with experience performing laparoscopic hernia repair. As reported above, proficiency with laparoscopic repair can generally be attained in 10 to 25 procedures. Reported operative times for laparoscopic unilateral inguinal hernia repair range from as little as seven minutes for a surgeon experienced in laparoscopic repair up to 55 minutes for a trainee or surgeon inexperienced with laparoscopic repair. Overall, a surgeon experienced in laparoscopy and proficient in the laparoscopic repair of inguinal hernias should have comparable operative times to a surgeon performing the standard open technique. In the case of bilateral hernias, the laparoscopic approach may be superior.

Complication Rates
Possible complications with both the laparoscopic and open repair include injury to cord structures, injury to nerves, hydrocele, testicular atrophy, testicular injury, and testicular malposition. Laparoscopic repair adds additional risk of major blood vessel or abdominal viscera injuries, most frequently due to insertion of trocars or Veress needle to establish pneumoperitoneum. While pediatric-specific data is sparse, data from the population at large suggests that these events are rare. Major blood vessel injury occurs at a rate between 0.03 and 0.3 percent, with an average rate of 0.1 percent. Abdominal viscera injuries, the vast majority of which are small or large bowel, occur at rates of 0.05 to 0.3 percent. The open repair is generally regarded as a safe procedure with low complication rates, but the current evidence suggests that the laparoscopic approach does not increase the risk of complications. This may be a result of laparoscopy eliminating the need to manipulate the vascular structures of the testes. Philippe et al. note a 0 percent rate of testicular atrophy or testicular malposition, compared to published rates of up to 2.7 percent for each in open repair. A prospective review by Dutta et al. of 275 laparoscopic hernia repairs indicated no spermatic cord injuries, no testicular atrophy, and no symptoms of ilioinguinal nerve injury. Overall, a number of studies have found that the safety and testicular complication
Top 2 Reasons
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In a recent survey among South Dakota women who didn’t get prenatal care as early as they wanted, two primary barriers were reported:

1. I did not know I was pregnant.

2. I could not get an appointment when I wanted one.

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Help us give every baby the best possible start to a healthy life.

rates of laparoscopic repair are no different when compared to the open technique. One randomized controlled study by Shalaby et al. reported a significantly lower rate (p<0.049) of iatrogenic ascent of the testes. Hydrocele and testicular atrophy occurred at rates that were not statistically different between procedures. When incarcerated tissue or bowel is present, laparoscopy may be superior to the open approach in the removal and evaluation of incarcerated tissue due to its excellent magnified view providing direct visual control, the ability to simultaneously apply external manual pressure while internally pulling, and the avoidance of dissecting an edematous hernia sac. The complication rates of laparoscopic repair remain at the same low level as the traditional open repair in the available literature. When incarcerated hernia is present, the complication rate of laparoscopy may be lower.

Postoperative Pain
Another consideration when evaluating laparoscopic repair versus open repair is the presence and degree of postoperative pain. One of the benefits of other laparoscopic and minimally invasive procedures is the potential for reduced postoperative pain. A randomized controlled trial by Chan et al. evaluated pain scores using the Children and Infants Postoperative Pain Score and the Children’s Hospital of Eastern Ontario Pain Score in 97 children older than three months undergoing laparoscopic and open inguinal hernia repair. The authors noted higher pain scores in the open repair group as well as significantly more analgesic doses required (p=0.032). Celebi et al. evaluated a visual analog scale of pain scores related to bilateral inguinal hernia repair. Pain scores were significantly higher (p=0.036) in the open repair group than the laparoscopic repair group at one hour postoperatively. During other recorded time frames, there were no significant differences in pain scores. Additionally, the authors showed no difference in requested or delivered analgesic doses per 24 hours. These findings are similar to the randomized controlled trial conducted by Bharathi et al. involving 85 children undergoing unilateral inguinal hernia repair that found no difference in postoperative pain. The meta analysis by Yang et al. found no significant difference in postoperative pain between laparoscopic and open repairs. In contrast, a prospective study of 89 children by Koivusalo et al. found that a significantly higher portion of the laparoscopic repair group required rescue analgesia postoperatively (79 versus 42 percent, p<0.05). Additionally, the laparoscopic group had a significantly higher median pain score on the second postoperative morning (p<0.05). This did not affect time to return to normal activity, the primary outcome of the study. The evidence for postoperative pain following laparoscopic and open repair of inguinal hernia presents a mixed picture. As a whole, it appears that there is no difference in postoperative pain between the two groups.

Cosmesis
One benefit of laparoscopic surgery over traditional open techniques is its ability to produce superior cosmesis. A number of studies indicate that the cosmesis achieved with laparoscopic repair of pediatric inguinal hernia is superior compared to the open approach. Koivusalo et al. indicated that the cosmesis provided by each technique is similar due to the location of the incision in the open approach. Philippe et al. asked patients and families to rank the residual scars following laparoscopic repair. Forty-five percent were considered “not visible” while an additional 49.4 percent were considered “barely visible.” When Celebi et al. compared bilateral inguinal hernia repair, parents of patients scored the wound appearance of laparoscopic repair significantly better than that of open repair (p<0.05). Overall, it is difficult to definitively say that the cosmesis provided by laparoscopic repair is superior to open repair, although there is evidence to suggest that it is, especially in the case of bilateral hernias.

Conclusions
Laparoscopic repair of pediatric inguinal hernias presents a viable alternative to the standard open repair. While pediatric surgeons are reluctant to adopt the use of the technique at a widespread level, there are several advantages to laparoscopy. These include superior visualization of the relevant anatomy, ability to assess and repair a contralateral hernia, lower rates of metachronous hernia, shorter operative times with surgeons experienced in laparoscopy, lower potential complication rates, and better cosmesis. There is similar recurrence rate and postoperative pain when comparing laparoscopic and open techniques. The major limitation in comparing open hernia repair to laparoscopic hernia repair is the lack of a single accepted best method for laparoscopic repair. Randomized controlled trials and large multicenter studies are lacking in the pediatric population. In order to definitively conclude that one technique is superior to the other, a single laparoscopic technique will need widespread acceptance and additional large randomized trials will need to be performed.

Acknowledgements: Special thanks to Dr. Sue Davies, PhD for her assistance in editing this article.
REFERENCES

2017 ANNUAL LEADERSHIP CONFERENCE

WHEN: Friday, June 2

8 am  Membership Meeting with Presentations from AMA Chair-Elect Dr. Gerald E. Harmon and SSOM Dean Dr. Mary Nettleman
9:15 am Membership Open Forum
10:45 am Panel Discussion: Physician Burnout
12 pm SDSMA PAC Lunch: Clinician Health and Wellbeing – Reducing the Cost and Impact of Physician Burnout
1:30 pm Council of Physicians Meeting
4:30 pm Policy Council Meeting
6 pm Membership Mixer
7 pm Awards Banquet & Scholarship Recognition

WHERE: SpringHill Suites & Cadillac Jacks, Deadwood

We hope to see you there – register today!
To register, visit www.sdsma.org.

Abstract
Consuming excessive amounts of alcohol has the potential to modify an individual’s brain and lead to alcohol dependence. Alcohol use leads to 88,000 deaths every year in the U.S. alone and can lead to other health issues including cancers, such as colorectal cancer, and mental health problems. While drinking behavior varies due to environmental factors, genetic factors also contribute to the risk of alcoholism. Certain genes affecting alcohol metabolism and neurotransmitters have been found to contribute to or inhibit the risk. Gene-environment interactions may also play a role in the susceptibility of alcoholism. With a better understanding of the different components that can contribute to alcoholism, more personalized treatment could cater to the individual. This review discusses the major genetic factors and some small variants in other genes that contribute to alcoholism, as well as considers the gene-environmental interactions.

Introduction
Craving, loss of control, physical dependence, and tolerance are symptoms of alcoholism, with the latter symptom resulting in a higher consumption of excess alcohol. Different genetic and environmental factors contribute to the level of alcohol consumption. Human twin studies have also provided support that certain responses to alcohol are due to genetic influence.\(^1\) While there are several genes known to contribute to the risk of alcoholism, it is important to consider environmental stressors and gene-environment interactions as well. It is beneficial to consider this gene-environment interaction along with the genes currently known to affect metabolic processes and neurotransmitters which in turn can lead to better treatment and prevention tactics.

Alcohol Metabolism
Alcohol metabolism consists of several oxidative pathways.\(^1\) Figure 1 depicts several main enzymes involved in alcohol metabolism. Alcohol dehydrogenase (ADH) metabolizes ethanol to produce acetaldehyde.\(^7\) Cytochrome P450 and catalase have the same function as ADH although these enzymes primarily play a role in metabolizing ethanol when there is a higher ethanol concentration or if there is hydrogen peroxide present, respectively. Acetaldehyde, the byproduct of above enzymes, is highly reactive and toxic and potentially contributes to the addictive process and tissue damage. Acetaldehyde can also form adducts with dopamine to make salsolinol, a possible contribution to alcoholism. Therefore, aldehyde dehydrogenase (ALDH) rapidly metabolizes acetaldehyde to produce acetate and NADH. ALDH2 is mainly involved in this process. The produced acetate then gets oxidized to carbon dioxide.\(^5\)

Figure 1. Primary enzymes involved in the oxidative pathways of alcohol metabolism. Alcohol dehydrogenase in the cytosol converts ethanol to acetaldehyde. Catalase in peroxisomes also oxidize alcohol in the presence of hydrogen peroxide. Cytochrome P450 mostly in microsomes are helpful at higher ethanol concentrations in metabolizing ethanol to acetaldehyde. Aldehyde dehydrogenase in the mitochondria metabolizes acetaldehyde into acetate.\(^5\)
Alcohol dehydrogenase and aldehyde dehydrogenase have been found to be associated with a higher risk of alcoholism. Looking specifically at alcohol dehydrogenase 1B (ADH1B), a specific coding variant rs1229984 is common in Asian populations. This variant replaces Arg48 with His48 and has been found to lower the risk of alcoholism in East Asian populations. In recent years, this variant was analyzed in European and African populations. Analyzing a population defined to be alcohol dependent, the His48 variant was found to have a significant association with a reduced risk for alcohol dependence with a similar magnitude of effect for both European and African populations. Another study involving a specific European population obtained blood samples and had participants complete a questionnaire which included drinking frequency and average alcohol intake. This population was randomly selected in contrast to the other study. An association between the ADH1B variant and the frequency and intake of drinking was found.

There are multiple studies that also support the trend of the ADH1B variant having an association with risk towards alcoholism. However, not much is known about the mechanism behind this association. A study in which male subjects having different ADH1B variants were administered different amount of doses of ETOH or a placebo was conducted. An association between the variant, blood ETOH, and acetaldehyde levels was found. This study provides the groundwork for further examining the protective mechanism of ADH1B variants.

Aldehyde dehydrogenase 2 (ALDH2) is a known protein encoding gene that is a part of the oxidative pathway for alcohol metabolism. As stated previously, ALDH2 plays a role in the essential step of oxidation of acetaldehyde to acetate. A variation of this gene has been found to be prevalent in Asian populations and thought to decrease the risk of alcohol dependence. The specific allele ALDH2*2 disrupts normal alcohol metabolism but few studies have looked at whether this effect is related to environmental context or the developmental stages.

Especially among East Asian populations, the ALDH2 variant has a lower oxidative efficiency. Due to this lower efficiency, acetaldehyde builds up in the tissues leading to such symptoms as a flushed face, headache, and nausea. In comparison to those without the variant, individuals with ALDH2*2 are less likely to become alcohol dependent. Oftentimes alcohol consumption will increase through the course of adolescence to adulthood. To determine the relationship between allele variants and environmental factors, a sampling of 356 adopted participants of Korean descent who carried the ALDH2*2 allele was done. As age increased, the protective effect of ALDH2*2 increased, as well. There was no correlation between the genotype and the initiation of alcohol use. Although in the adopted participants, parental drinking habits either strengthened or weakened the protective effect of ALDH2*2 suggesting that there is a gene-environment correlation for ALDH2 as the parents did not carry the ALDH2*2 allele. More recent studies have further supported that the ALDH2*2 allele in East Asians cause physical symptoms and that there may be a more complex gene-environment correlation involved.

Further examining these genes and their respective variants not only could provide more information on the risk of alcoholism, but also the risk for other health issues. Alcohol is one of the risk factors for colon cancer. In recent years, an observed study population of 3,545 individuals observed an association between the ADH1B polymorphism and colorectal cancer risk. Another recent study conducted in Japan suggested an influence from polymorphisms in both ADH1B and ALDH2 on the development of colorectal tumors.

**GABA Receptors**

Animal models have shown evidence of the γ-aminobutyric acid (GABA) receptor A (GABRA) regulating alcohol self-administration. Genome-wide scans for humans have also provided additional evidence linking alcoholism to genes encoding GABRA subunits. An analysis using Study of Addiction: Genetics and Environment (SAGE) data and genome-wide association studies (GWAS) data sets found that some single-nucleotide polymorphisms (SNPs) of GABRA are associated with alcoholism. Five GABA receptor genes were analyzed with alcohol dependence and the meta-analysis suggested that the GABA receptor gene, GABRA2 (γ-aminobutyric acid A receptor α2 subunit gene), is involved in the development of alcoholism. GABRG2 and GABRA6 were also found to have an association with alcohol dependence. GABRA2 was additionally found to be associated with alcohol dependence through SAGE and GWAS data sets.

Using the in vivo method known as the alcohol clamp, alcohol was distributed to the study population through intravenous infusion. The findings showed that GABRA2
alleles play a role in alcohol usage risk. More specifically, seven SNPs were included in the analysis and three (rs279869, rs279858, and rs279837) that are located in the middle of the GABRA2 gene were shown to have significant associations with subjective responses to alcohol.\textsuperscript{1}

Although the molecular mechanism for GABRA2 and its association with alcoholism is not fully understood, the usage of induced pluripotent stem cells (iPSCs) as a model system provides insight on the correlation in human neural cells. The mRNA expressions on chromosome 4p12 GABA\textsubscript{A} subunit genes (which includes GABRA2) in iPSC differentiated human neural cell lines suggested that genotype effects on GABA\textsubscript{A} expression associated with alcoholism has an effect on regulation of the cluster of subunit genes on the chromosome of interest during neural development.\textsuperscript{18}

**Corticotropin-Releasing Hormone Receptor 1 (CRHR1)**

The CRHR1 gene has been found to interact with stress and modulating excessive alcohol consumption.\textsuperscript{19} A particular CRHR1 gene variant was found to influence response to negative emotional stimuli. The gene variant, rs110402, was observed through fMRI to influence negative emotional words in the right ventrolateral prefrontal cortex. This variant also was found to be involved in the internalizing negative affect pathway, therefore modulating the risk of problem drinking.\textsuperscript{20}

Previously, the ALDH2*2 allele was introduced as being present in primarily East Asian populations. Keeping that in mind, a study included participants of exclusively Korean descent. Similarly, the results suggested that the CRHR1 gene is an important genetic factor in the cause/risk of alcoholism. However, the CRHR1 gene variants observed in this study were different from the previous study.\textsuperscript{21} This suggests the possibility of several CRHR1 gene variants to be involved in the interaction between stress and alcoholism.

**Gene-Environment Interaction**

Heritability of alcoholism has been estimated in approximately 50 percent of those who fulfill the criteria for alcohol dependence. This suggests that both genetic and environmental factors are involved.\textsuperscript{19} Alcoholism, in part due to its classification as a type of addiction, is a chronic, relapsing disorder. For alcoholics, an observable characteristic includes a negative emotional state which leads to a higher susceptibility to stress. Stress and alcohol cues were found to cause neural changes in the brain through fMRI imaging.\textsuperscript{22} However, the connection between stress and alcohol is complex and not quite understood. Both animal and human studies have been conducted in order to provide a better understanding of this relationship. Various studies found that chronic stress resulted in elevated drinking later in adulthood.\textsuperscript{23} Alcohol exposure was also observed to be a stressor itself causing an increase in voluntary alcohol consumption.\textsuperscript{24}

**Conclusion**

Alcohol addiction has a heavy impact on our society and any advancements to reduce this burden would be welcome. There is evidence supporting genetic factors having an association with alcoholism. However, the subject and extent of the genetics is a topic of interest that is still being researched and studied. Keeping in mind not only the genetic influences, but the gene-environment interactions in addition will be beneficial in future endeavors for understanding and handling this type of addiction.
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Membership Mixer
6:00 pm

Awards Banquet & Scholarship Recognition
7:00 pm

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Antimicrobial resistance is threatening available treatment options and accounts for 23,000 deaths annually.¹ The top offending organisms include multiple-drug resistant (MDR) Acinetobacter and Pseudomonas aeruginosa, extended-spectrum β-lactamase (ESBL) and carbapenem-resistant Enterobacteriaceae. Nearly 900 unique β-lactamas provide the mechanism of resistance for MDR gram-negative infections.² The established cephalosporin, ceftazidime, has extended gram-negative coverage when combined with the new β-lactamase inhibitor avibactam therefore providing a treatment option for MDR organisms.³ Ceftazidime-avibactam (Avycza) received marketing approval from the Food and Drug Administration (FDA) in February 2015 for treatment of complicated intra-abdominal infections (cIAI) with concomitant metronidazole and complicated urinary tract infections (cUTI) caused by resistant gram-negative organisms.⁴

**Chemical Structure and Mechanism of Action**

Ceftazidime is a semisynthetic, β-lactam, third-generation cephalosporin exhibiting affinity for penicillin binding proteins (PBP).⁵ The overall activity is bactericidal by disruption of cell wall synthesis. Much of ceftazidime’s activity is isolated to PBP 3 of P. aeruginosa and Escherichia coli. Several bacteria develop β-lactamases to hydrolyze and disrupt the classic 4-membered rings of the β-lactam antimicrobials, making these agents less effective.⁶ Adding β-lactamase inhibitors allows various β-lactam antibiotics to retain antimicrobial activity. In combination, avibactam protects ceftazidime from degradation by serine β-lactamases to preserve activity against clinically significant gram-negative organisms. Avibactam is a diazabicyclooctane, non-β-lactam β-lactamase inhibitor with no direct antimicrobial activity. The extended spectrum to various MDR organisms is likely due to the activity at the serine site, avibactam forms a highly stable carbamoyl link disabling the catalytic activity of the serine residue.⁷

**Spectrum of Activity**

Ceftazidime-avibactam demonstrates time-dependent bacterial killing at greater than two-times the minimum inhibitory concentration (MIC).⁵ Avibactam is capable of inhibiting Class A, C, and variable D β-lactamases. Coverage includes extended spectrum β-lactamases (ESBL), AmpC-mediated resistant P. aeruginosa, and carbapenemases (Table 1).

<table>
<thead>
<tr>
<th>High Susceptibility</th>
<th>Minimal Susceptibility</th>
<th>Clinical Significance Unknown</th>
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<tbody>
<tr>
<td>Citrobacter freundii</td>
<td>K. oxytoca (ESBL)</td>
<td>Morganella morganii</td>
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<tr>
<td>Citrobacter koseri</td>
<td>K. pneumoniae (ESBL)</td>
<td>Providencia stuartii</td>
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<tr>
<td>Enterobacter aerogenes</td>
<td>K. pneumoniae carbapenemase</td>
<td>Providencia rettgeri</td>
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<td>Enterobacter cloacea</td>
<td>Proteus spp (ESBL)</td>
<td>Serratia marcescens</td>
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<td>E.coli (ESBL)</td>
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<td>H. influenza</td>
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The combination remains inactive against class B metallo-β-lactamase organisms, demonstrates minimal activity against most Acinetobacter species, and variable susceptibility to anaerobes with the most notable being Prevotella spp.³ Organisms with overexpressed efflux pumps or porin mutations may not be susceptible to ceftazidime-avibactam.⁴ The addition of avibactam provides no additional gram-positive coverage compared to ceftazidime alone.¹

**Literature Review**

Two identical, randomized, double-blind phase 3 studies evaluated safety and efficacy of ceftazidime-avibactam plus metronidazole (n = 520) compared to meropenem (n = 523) in the treatment of cIAI. Baseline characteristics were similarly matched according to age, race, gender, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE) score, primary diagnosis, renal function, and infection type. A majority of the patients with a ceftazidime-resistant, gram-negative pathogen (ceftazidime-avibactam plus metronidazole,
n=47; meropenem, n=64) grew E. coli and K. pneumoniae. The primary endpoint evaluated clinical cure at day 28-35 and ceftazidime-avibactam was considered noninferior to meropenem if achieving a between-group difference with the lower limit of a 95 percent confidence interval (CI) greater than -12.5 percent. Clinical response was similar in the treatment of ceftazidime-resistant organisms (ceftazidime-avibactam plus metronidazole, 83 percent; meropenem, 85.9 percent). Patients with moderate renal function (CrCl 31-50 mL/min) experienced decreased clinical cure rates with ceftazidime-avibactam plus metronidazole treatment compared to meropenem 72 percent and 88 percent, respectively. Ceftazidime-avibactam plus metronidazole treatment was noninferior to meropenem and displayed similar efficacy compared to ceftazidime against ceftazidime-susceptible cIAI. No new safety considerations were identified in these studies.7

Two identical, randomized, multicenter, double-blind, double-dummy, parallel-group phase 3 studies evaluated the safety and efficacy of ceftazidime-avibactam (n = 393) compared to doripenem (n = 417) in the treatment of cUTI. Baseline characteristics were similarly matched according to age, race, gender, BMI, diagnosis, renal function, and pathogen. Patients were randomized 1:1 to either ceftazidime-avibactam 2.5 grams every eight hours or doripenem 500 mg every eight hours. Primary endpoints evaluated the proportion of patients with resolution of symptoms, excluding flank pain, at the five-day follow-up and the proportion of patients with infection eradication and symptom resolution at 21-25 days. Noninferiority was determined by a treatment difference with the lower limit of a 95 percent CI greater than -12.5 percent. Ceftazidime-resistant organisms consisted mostly of E. coli and K. pneumoniae (ceftazidime-avibactam, n=75; doripenem n=84). Resolution at five-day follow-up occurred in 70.2 percent of ceftazidime-avibactam and 66.2 percent of doripenem while infection eradication at 21-25 days occurred in 77.4 percent and 71 percent, respectively. Favorable microbiological response rates were similar between ceftazidime-avibactam (64 percent) and doripenem (60 percent) in the treatment of ceftazidime-resistant organisms. Overall, the study suggests ceftazidime-avibactam is an alternative therapy option for patients with cUTI, particularly caused by ceftazidime-resistant and carbapenemase organisms.8

The REPRISE trial, a randomized, pathogen-directed, international, phase 3 study evaluated ceftazidime-avibactam compared to the best available therapy for the treatment of cIAI or cUTI caused by ceftazidime-resistant E. coli, K. pneumoniae, Enterobacter cloacae and P. aeruginosa. The 333 recruited patients were randomized 1:1 to ceftazidime-avibactam 2.5 grams intravenously (IV) every eight hours or the best available therapy (97 percent being a carbapenem). Patients were similarly matched according to age, race, gender, BMI, renal function, pathogen, and infection type. The cIAI group was composed of relatively small numbers (ceftazidime-avibactam, n=10 and best available treatment, n=11) and a substantially larger group observed for cUTI (ceftazidime-avibactam, n=144 and best available treatment, n=137). The Jeffery method was used to calculate a two-sided 95 percent confidence interval with no formal set power. The primary endpoint evaluated clinical response (cure, intermediate, or failure) at seven to 10 days following the last day of treatment. A high proportion of clinical cure (91 percent) resulted in both treatment groups, supporting the use of ceftazidime-avibactam as an alternative to carbapenems in resistant gram-negative infections. This study provided safety and efficacy results consistent with previous evaluations of ceftazidime-avibactam.9

### Dosage and Administration

Ceftazidime-avibactam FDA approved dosing is 2.5 grams IV every eight hours with a two-hour infusion time. Treatment of cIAI, with concurrent metronidazole, is recommended for five to 14 days, while treatment of cUTI is recommended for seven to 14 days. The Cockcroft-Gault formulation is used to estimate renal function for dose adjustments (Table 2).4

<table>
<thead>
<tr>
<th>Estimated Creatinine Clearance (CrCl)</th>
<th>Dose Modification</th>
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<tbody>
<tr>
<td>&gt; 50 mL/min</td>
<td>No adjustment necessary</td>
</tr>
<tr>
<td>31-50 mL/min</td>
<td>1.25 grams every 8 hours</td>
</tr>
<tr>
<td>16-30 mL/min</td>
<td>0.94 grams every 12 hours</td>
</tr>
<tr>
<td>6-15 mL/min</td>
<td>0.94 grams every 24 hours</td>
</tr>
<tr>
<td>≤ 5 mL/min</td>
<td>0.94 grams every 48 hours</td>
</tr>
</tbody>
</table>

The original package labeling identified the components of the individual agents, ceftazidime 2 grams and avibactam 0.5 grams. However, due to confusion with dose adjustments recommendations are based on total grams.6 Due to concerns regarding potential dosing errors, the package labeling now identifies the strength as a combination of
the products with 2.5 grams on the vial. There is lack of safety and efficacy data to guide dosing in pregnancy, lactation and children less than 18 years old.4

Adverse Effects, Warnings and Precautions

Ceftazidime-avibactam is generally well tolerated with less than 10 percent occurrence of diarrhea, nausea, vomiting, headache, dizziness and abdominal pain in trials.4

Patients with renal function of CrCl 30-50 mL/min, experienced decreased efficacy in the treatment of cIAI. Patients in this subgroup were potentially under treated with doses 33 percent lower than recommended doses.

Hypersensitivity reactions may occur in those with previous penicillin allergies.

Clostridium difficile-associated diarrhea has occurred in patients treated with ceftazidime-avibactam.

Seizure and other neurologic effects may occur. Patients with renal impairment and inappropriate dosing adjustments are at increased risk.

Drug Interactions

When ceftazidime-avibactam is administered at clinically relevant concentrations, in vitro studies show neither induction nor inhibition of cytochrome P450 isoforms, hepatic, or renal transporters. Avibactam is a substrate of the OAT1 and OAT3 hepatic transporters and exhibited 56-70 percent reduction in uptake with concomitant probenecid. Therefore, probenecid increases levels of avibactam and co-administration is not recommended.4

Laboratory Test Interactions

Administration of ceftazidime-avibactam may interfere with laboratory results including Coombs test and urine glucose. In clinical trials, ceftazidime-avibactam caused a greater number of seroconversion from negative to positive direct Coombs test compared to carbapenems. Enzymatic glucose oxidase reaction is the preferred testing method to assess urine glucose to avoid false-positive results common to ceftazidime.5

Conclusions

The combination of the third generation cephalosporin ceftazidime with the non-β-lactam β-lactamase inhibitor avibactam provides an effective option for treatment of cIAI and cUTI. Ceftazidime-avibactam is a treatment option for select MDR gram-negative infections, particularly in situations of carbapenem resistant Enterobacteriaceae when alternative treatments are limited.

Ceftazidime-avibactam is not active against all β-lactamases thus initial susceptibility testing can identify candidates for ceftazidime-avibactam treatment. Appropriate antimicrobial stewardship should reserve the use of ceftazidime-avibactam to patients with few or no alternative treatment options and promptly modify treatment when culture and sensitivities become available.

REFERENCES

Antimicrobial resistance is one of the most significant public health threats in the U.S. with an estimated 2 million infections and 23,000 deaths yearly due to resistant organisms. As much as 30 percent of antibiotic use may be unnecessary, perhaps even higher in the outpatient setting. Antibiotic resistance infections are costly in terms of morbidity, mortality and financial burden.

Simply defined, antimicrobial stewardship is the process of encouraging the timely administration of antimicrobial agents. This has been made a priority for the Center for Disease Control and Prevention (CDC). With support from the White House to multiple state and local health agencies, the CDC is leading efforts to curb resistance and foster the timely administration of antimicrobials. The choice of drug, dosing and length of treatment are core elements of appropriate use. Overuse is obviously a major concern, but certain situations such as sepsis or bacterial pneumonia require rapid assessment and initiation of these agents.

Usage is easier to monitor in an inpatient environment through medical records, culture results and continuous evaluation of patient status. The outpatient environment is more difficult to track and assess. Clinics, including primary care and specialty along with acute and retail urgent care facilities, administer and prescribe antibiotics. Emergency departments and surgery centers are capable of delivering parenteral antimicrobial agents and would also benefit from a stewardship perspective.

In addition to physicians; nurse practitioners, physician assistants, dentists and veterinarians prescribe these agents and need to play a role in antibiotic stewardship. Pharmacists provide a valuable resource for prescribers in the complicated process of multiple medications, interactions and dosing variability. Their assistance is necessary for the process to improve usage and promote patient safety.

Antimicrobial stewardship, though present for some time, will likely require a continuous culture change in many prescribers due to their historical perspective and experience in treating suspected bacterial infections. When they were a developed, antimicrobial agents became a tool of significant improvement in health care. Today, however, knowledge gaps exist regarding medication resistance and interventions to prevent transmission of resistant organisms. Determining the appropriate diagnoses of when antibiotics are truly needed and for how long remains a challenge. It is beneficial to keep families apprised of the patient status if the condition is one of “wait and watch” before blindly beginning antibiotic therapy for uncertain conditions. It is important to document that the provider is monitoring the condition of the patient.

The random use of broad spectrum antimicrobials for extended periods of time leads to overuse and misuse. The consequence of such activity has led to significant healthcare associated infections (HAI), c. difficile infections and resistance to multi resistant organisms. Providers can benefit from knowledge gleaned from local antibiograms and frequent reassessment of culture sensitivities to help guide their choice of antibiotics. The South Dakota Department of Health is deeply involved in this area and their website offers stewardship resources for healthcare facilities at all levels, especially in long-term care. They have fostered an Antimicrobial Stewardship Workgroup that allows multiple organizations an opportunity to coordinate efforts in this ongoing struggle: https://doh.sd.gov/diseases/haistewardship.aspx.

The Great Plains Quality Innovation Network (QIN) has a quality improvement initiative for Combating Antibiotic Resistance through Antibiotic Stewardship in Communities. We hope to recruit providers and spread the principles of antimicrobial stewardship in the clinic and outpatient setting. This would include activity in the Four Core Elements: 1) commitment, 2) action for practice and policy, 3) tracking and reporting and 4) education and expertise. The Great Plains QIN Learning and Action Network (LAN) will provide access to tools, resources, education and subject matter experts. This is an opportunity to network and learn from the experience of others with similar interests and goals. This project is mainly educational and not structured to burden providers with excessive time or mandatory reporting. The aim is to provide a platform for outpatient antibiotic prescribing that will, hopefully, reduce unnecessary use. Please contact Cheri Fast at Cheri.Fast@area-A.hcqis.org if you have interest in this activity. Ongoing efforts at appropriate use will need to disseminate into the outpatient and long-term care settings in order to deliver appropriate antibiotic stewardship. Feel free to contact me in reference to the above mentioned activities at stephan.schroeder@area-A.hcqis.org.
Your referrals make a difference.

Healthcare providers play a huge role in helping tobacco users quit.

We know your recommendations and referrals make a difference. That’s why we have created some new tools to help keep you up to date.

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- Training Opportunities
- Webinars
- Cessation Medication Information
- Special Provider FAQ

We’ve also expanded our services to help make it easier for you to connect your patients to our services. Tobacco users can always call the QuitLine to enroll or request a call from us and now they can also:

- Receive a free 2-week Nicotine Replacement Therapy (NRT) Kickstart Kit
- Receive a free Quit Guide in the mail
- Check out our new Do It Yourself Self Help section

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March basketball tournaments were bouncing along the TV screen when a player fell. The replay showed how one fellow was shoved off balance and came down trying to stop his fall. The camera was watching as his ankle gave way and the foot turned inward. When he stood again, he was limping and I could almost feel his pain, made more obvious by the disappointment on his face. It was unavoidable, he was out of the game and tournament with an injured ankle.

I don’t know for sure, but I imagine the trainer examining his foot and noting no deformity, making it less likely to be a broken bone. As the examiner feels the outside areas of the ankle, I can almost hear the player admonishing the trainer. “Stop it. That’s where it hurts.” As the player’s foot turned in, most likely one or more of the three outside ligaments were stretched and possibly torn.

Ligaments are the very tough fibrous tissue that connect bone-to-bone, which are different than tendons, connecting muscle-to-bone. In this player’s case, it’s likely the ligaments involved were those that tie the outer bone of the lower leg to the ankle bones of the foot and that are meant to keep the ankle from turning too far inward. Ligaments between bones are strong bonds and allow for minimal movement while preserving stability. Test your own ankle movement by repositioning the ankle side-to-side or inward and outward. Note how limited that motion is when compared to the up and down movement of the foot as the calf muscles and Achilles tendon push you off, helping you walk or run.

Without the side-to-side stability ligaments, the foot would not be capable of normal walking on irregular ground, let alone the running, turning, and leaping required to play in a basketball game. What is almost more incredible is how pain from such an injury forces us to rest and protect the ankle so it can heal.

The treatment for this injury and for almost any ligament or tendon injury, is directed by the mnemonic RICE. R is for rest, I for ice, C for compression wrap, and E for elevation. Most certainly, the trainer will use those directives and over the next two weeks, the player will gradually move back to careful and easy walking once again. In about six weeks, 90 percent of the healing will be achieved.

Next season he will be ready to play again.
FOR MORE INFORMATION
on how to donate to the SDSMA Foundation, which raises money for scholarships
at the University of South Dakota Sanford School of Medicine, visit www.sdsm.org.
For Your Benefit:

Providing Solutions for Your Practice

The SDSMA provides practice management consulting at below-market prices, hands-on help with payment problems and a comprehensive array of services to help you take care of the business side of your practice.

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- Legal briefs are available to SDSMA members on SDSMA’s website, www.sdsm.org.

The challenges of practicing medicine have never been greater, and the added challenges of administering a practice can be daunting. We can help. Give us a call at 605.336.1965, or visit our website today at www.sdsm.org.

We are grateful for your attention and appreciate the trust you have placed in us. Thank you for being a member of the SDSMA.

“For Your Benefit” is the Association’s monthly update on programs and services available to physicians through their affiliation with SDSMA.

Registration Deadline Approaching – 2017 SDSMA Annual Leadership Conference

The 2017 SDSMA Annual Leadership is in Deadwood on Friday, June 2. The May 19 deadline to register is quickly approaching.

With presentations, discussions, networking opportunities and social events, the Annual Leadership Conference is a great time to share ideas and learn from fellow members.

Check out the schedule and events! Do you have a policy issue you’d like to bring to the SDSMA’s attention? Learn how to address the Council at www.sdsm.org. Members have until May 5 to submit issues for consideration.

The Annual Leadership Conference is a benefit of your membership. For the latest details about exciting events taking place during the 2017 SDSMA Annual Leadership Conference, visit www.sdsm.org. Buy your tickets for the banquet and SDSMA PAC lunch online.

Those who need a hotel room may call SpringHill Suites at 605.559.1600 or Cadillac Jacks at 605.578.1500 and ask for the South Dakota State Medical Association block.

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<tr>
<th>SCHEDULE</th>
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<tbody>
<tr>
<td>8 am</td>
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<tr>
<td>Membership Meeting with presentations from AMA Chair-Elect Gerald E. Harmon, MD and SSOM Dean Mary Nettlem an, MD</td>
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<tr>
<td>9:15 am</td>
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<tr>
<td>Membership Open Forum</td>
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<tr>
<td>10:45 am</td>
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<tr>
<td>Panel Discussion: Physician Burnout</td>
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<tr>
<td>12 pm</td>
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<tr>
<td>SDSMA PAC Lunch: “Clinician Health and Wellbeing – Reducing the Cost and Impact of Physician Burnout”</td>
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<tr>
<td>1:30 pm</td>
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<tr>
<td>Council of Physicians Meeting</td>
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<td>4:30 pm</td>
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<tr>
<td>Policy Council Meeting</td>
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<td>6 pm</td>
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<td>Membership Mixer</td>
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<tr>
<td>7 pm</td>
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<tr>
<td>Awards Banquet &amp; Scholarship Recognition</td>
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Physician Burnout is Topic of SDSMA PAC Lunch

During the SDSMA Annual Leadership Conference, the SDSMA PAC will feature a speaker on the topic of physician burnout.

The SDSMA PAC lunch presentation, “Clinician Health and Wellbeing – Reducing the Cost and Impact of Physician Burnout,” will be held from 12-1:30 pm Friday, June 2 at the SpringHill Suites & Cadillac Jacks in Deadwood. The speaker will be Laurie Drill-Mellum, MD, MPH, chief medical officer and vice president of safety solutions at MMIC.

SDSMA PAC Lunch tickets are $40 and are available at www.sdsma.org. Please purchase your tickets by May 19.

It’s not too late to register for all of the activities taking place during the Annual Leadership Conference – find more information at www.sdsma.org.

Membership Mixer is Networking Opportunity

Members are invited to the SDSMA’s Membership Mixer from 6-7 pm Friday, June 2 at SpringHill Suites/Cadillac Jacks during the 2017 SDSMA Annual Leadership Conference.

Enjoy a unique and fun opportunity to meet SDSMA leaders and network with your peers. Meet other physicians in the state to expand your professional network and share ideas. The event is sure to be an all-around great time! Spouses are welcome to attend. Drinks and hors d’oeuvres will be served.

The mixer is free of charge. Tickets are required for the Awards Banquet & Scholarship Recognition following the mixer. To buy banquet tickets, please visit www.sdsma.org or call 605.336.1965.

Join Us for Awards Banquet & Scholarship Recognition

Enjoy a fun-filled evening of celebration Friday, June 2 at the 2017 SDSMA Annual Leadership Conference at SpringHill Suites/Cadillac Jacks in Deadwood.

Start the evening with the Membership Mixer at 6 p.m., and continue the celebration at the Awards Banquet and Scholarship Recognition, where Robert E. Van Demark, Jr., MD, will be sworn in as SDSMA president, awards will be bestowed upon fellow colleagues, outgoing and incoming officers will be celebrated and welcomed, and medical student scholarship recipients will be recognized.

The mixer is free of charge; banquet tickets are $65 and must be purchased in advance. To buy tickets and register for other annual meeting activities, visit sdsma.org. Please purchase tickets and register by May 19.

Legal Brief Highlight: Venereal Disease

Syphilis, gonorrhea, and chancroid, venereal diseases must be reported to the appropriate public health officials and treatment for the disease may be required by state, county or municipal health officials. Physicians must take a blood sample from every pregnant woman to test for syphilis. The occurrence of the test must be recorded upon the birth or stillbirth of the child. Upon receipt of consent from parents or guardians, minors may be treated. Minors may seek treatment, absent such consent, from county or state health departments.

For more information, download the SDSMA legal brief Venereal Disease at www.sdsma.org. Through the SDSMA Center for Physician Resources, the SDSMA has developed more than 50 legal briefs that are available to members. In addition, the Center develops and delivers and programs for members in the area of practice management, leadership and health and wellness.
AMA, Other Organizations Send Letters to Trump & Congressional Leaders

The American Medical Association and other organizations representing insurers, hospitals, health plan purchasers, have sent letters to President Trump and Congressional leaders urging them to address an imminent threat to the stability of the individual health insurance market.

Cost-sharing reduction subsidies for certain low-income enrollees in marketplace exchange plans have been financed through payments made to insurers by the U.S. Department of Health and Human Services. These subsidies reduce out-of-pocket costs for patients who might otherwise be unable to afford health care services despite being insured. The U.S. House of Representatives sued the Obama Administration over the way these payments were financed – without specific appropriations by Congress. A district court held that the cost sharing payments were, in fact, unconstitutional, but stayed an injunction on making the payments to avoid a collapse of the marketplace while the administration appealed the decision. After the elections, the House successfully petitioned the appeals court to put the case on hold, arguing that significant health care policy changes were imminent, but absent significant movement on health system reform legislation the appeals court will likely move forward in coming months. Since the law requires insurers to finance these subsidies regardless of whether they receive federal payments to do so, they would face enormous financial losses and leave the market, leaving millions of Americans without insurance and likely causing disruptions throughout the system.

The letters ask policymakers to act quickly to ensure that these cost sharing reduction payments continue while broader marketplace stabilization efforts are developed.

Source: AMA

“The Issue Is” is the SDSMA’s monthly update on key policy issues of importance to physicians.
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