Contents

President’s Comments
195 You’re Invited to the SDSMA Annual Leadership Conference May 31
– Christopher T. Dietrich, MD

Editorial
196 Maternal Mortality in the U.S. and South Dakota
– Erica Schipper, MD, FACOG

The Journal
200 Squamous Papilloma After Endoscopic Ablation of Barrett’s Esophagus:
A Case Report and Review of Literature – Mohamed A. Abdallah, MD;
Muslim Atiq, MD; Jeffrey Murray, MD; Bhareshkumar J. Patel, MD
203 Giant Tubulopapillary Apocrine Cystadenoma with Mucinous Metaplasia
– Anna B. Bahnson, MD; T. Joel Tjarks, MD; Amy M. Kerkvliet, MD
206 A County-Level Health Index to Capture Geographic Variation in Health
Conditions in North Dakota, South Dakota, and Minnesota – Jing Zhao, PhD;
Tess Weber, MPH; Jessica Hanson, PhD; Morgan Nelson, MS;
Chad Birger, MS; Susan Puumala, PhD
214 Development of Leiomyosarcoma in a Patient Treated with Azathioprine
– Mohamed Abdallah, MBBS; Mohamed Saleh, MD; Hesham Elgouhari, MD;
Mark K. Huntington, MD, PhD

Primers in Medicine
218 Pulmonary Hypertension: Brief Review Article – Ahmed Gohar, Md;
Anup Shrestha, MD; Adam Stys, MD
226 Overview and Management of Small Bowel Obstruction versus Ileus: A
Primer for All Physicians – Jesse Van Maanen, MD; Hassan Turaihi, MD;
Paula Denevan, MD; Thavam Thambi-Pillai, MD, MBA, FICS, FACS

Pharmacology Focus
232 Use of Oral Antibiotics in Deep-Seated Infections: A Paradigm Shift
– Janet R. Fischer, PharmD; Kimberly A. Messerschmidt, PharmD;
Shannon Jo Miller, PharmD

Special Features
235 Board News – Margaret B. Hansen, PA-C, MPAS
236 Quality Focus: Changes and Challenges in Long-Term Care
– Stephan D. Schroeder, MD, CMD, CMQ
237 Patient Education: Fearing Death Can Cause Suffering – Richard P. Holm, MD
238 Member News

Advertisers In This Issue
240 Physician Directory
Strengthening Marital Bonds with Orange Juice

WALT MOZDZER, CFP®, CAP®, Lead Advisor

Every week, I trudge into a natural grocery store and buy a 32-ounce container of fresh-squeezed orange juice for my wife. Before I enter the store, Janna inevitably reminds me, don’t forget the O.J. Now that’s one of several items I buy, so it is not a single purchase event. But the juice is a symbol of my affection for her and a metaphor for marital contentment. In buying Janna orange juice, both of us are getting what we want financially... let me explain.

Several years after we were married, I learned through family stories that growing up, Janna would receive a “thimble-sized” glass of orange juice at breakfast. She begged for a bigger glass but was denied, because “orange juice was expensive” and money was tight.

As an adult, this mild deprivation led to her taking on the role of spender in our marriage. Perhaps the pent-up demand for orange juice morphed into an equivalency around “buying stuff equals happiness.” On the other hand, I pinned my financial security on a strong sense of frugality, sensibility, and a habit of saving.

My parents sacrificed their personal lifestyles to invest in an education for me and my brother. Their clothes were often worn, and my school clothes were mostly purchased at a thrift store. I realized from a young age that money was not something you spent in a wasteful manner. If we didn’t have the cash, we didn’t purchase it.

What’s interesting is that both of our parents had thrifty mindsets. Yet, I turned out one way and Janna another. How did this happen? Nature versus nurture? Probably a bit of both. That’s for the behaviorists to figure out.

The constant undercarriage of tension around money went on for years, until I finally realized the only way to both get what we wanted was for me to give in on relatively small purchases that bring her frequent joy.

This year, we’ll celebrate 25 years of marriage. Although the road to progress is not always as smooth as youthful expectations, the wisdom and perspective I’ve gained through the process has given me confidence and a sense of peace about our future. Janna and I are very different people with very different perspectives. The tapestry of life is layered with small decisions and experiences that bring us joy, sadness, disgust, surprise, fear, and humor. The orange juice brings weekly delight for both of us.

WE MIGHT NOT SEND YOU FLOWERS “JUST BECAUSE.”

But we do know how to keep our relationship fresh.

At Foster Group, the honeymoon is never over. We want our clients to feel Truly Cared For™ – whether they’ve been a client for days or decades. We’re an independent, fee-only firm with an integrated approach to financial planning and investment management, and our fiduciary responsibility keeps us focused on client needs.
It is my pleasure to invite you to the 2019 SDSMA Annual Leadership Conference. The event is in Sioux Falls on May 31 with all activities taking place at the Hilton Garden Inn Downtown. Those who wish to attend can register for all activities and buy tickets for the lunch and banquet at sdsm.org. Please register by May 20.

At this year’s conference, we are featuring speakers on the topic of violence and healthcare. Below is a listing of the full schedule including the presentations where we are happy to welcome many experts in this field. The Annual Leadership Conference is a benefit of your SDSMA membership – conference registration is free to members.

For lunch, the SDSMA PAC will welcome Greg DeSautel, MD, secretary of the South Dakota Department of Social Services. Dr. DeSautel was appointed by Gov. Kristi Noem in January 2019. The South Dakota Medicaid program provides health care to approximately 14 percent of all South Dakotans – the majority, 68 percent, of which are children. Dr. DeSautel will share with the audience his thoughts regarding the Medicaid program and its priorities.

I also encourage members to attend the open forum which will be held at 1:30 pm. This is an opportunity to hear from the membership regarding policy issues they’d like to bring to the SDSMA Policy Council’s attention and helps shape our policy for the coming year. Please schedule your time to address the Council in advance. More information about submitting a policy issue can be found at sdsm.org.

Members are invited to the SDSMA’s Membership Mixer and banquet beginning at 6 pm. The mixer is a 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. Spouses are welcome to attend. Drinks and hors d’oeuvres will be served. We will then continue our celebration at the banquet, where Robert J. Summerer, DO, will be sworn in as SDSMA president, awards recipients will be announced, outgoing and incoming officers will be welcomed, and medical student scholarship recipients will be recognized. Keep checking back at sdsm.org for additional details and updates.

Those who need a hotel room may call the Hilton Garden Inn at 605.444.4704 and ask for the South Dakota State Medical Association block or find a link to the Hilton’s SDSMA reservation homepage at sdsm.org.

Thank you for the opportunity to serve as SDSMA president over the last 12 months. It has been an exciting year and I look forward to what the SDSMA has in store as we continue moving into the future.

Annual Leadership Conference Schedule

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>8 am</td>
<td>Update from American Medical Association – David O. Barbe, MD, MHA, Past President, AMA</td>
</tr>
<tr>
<td>8:45 am</td>
<td>“What is Predictable is Preventable: Fostering Resilience and Recover in the Face of Trauma” – Charity H. Evans, MD, MHCM, FACS, Trauma Surgeon, Nebraska Medicine/University of Nebraska Medical Center; Founder, Dusk to Dawn Youth Violence Prevention Program, Omaha</td>
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<tr>
<td>9:45 am</td>
<td>“A Pandemic of Violence: The Role of Health Care Providers in Preparedness and Response (With an Assist from W. Shakespeare)” – James J. James, MD, PhD, MHA, Executive Director, Society for Disaster Medicine and Public Health; Editor-in-Chief, Disaster Medicine and Public Health Preparedness</td>
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<tr>
<td>10:45 am</td>
<td>Panel Discussion: The Impact Violence has on the Health Care Community – Brad Archer, MD; Mike Elliott, MD; Charity Evans, MD; Blake Gustafson, MD; Jim James, MD; Matt Owens, MD; Matthew Sorrell, MD</td>
</tr>
<tr>
<td>11:45 am</td>
<td>Update from the University of South Dakota Sanford School of Medicine – Tim Ridgway, MD, Executive Dean/Dean of Faculty Affairs, USD SSOM</td>
</tr>
<tr>
<td>12:15 pm</td>
<td>SDSMA PAC Lunch: Greg DeSautel, MD, Secretary, South Dakota Department of Social Services</td>
</tr>
<tr>
<td>1:30 pm</td>
<td>Membership Open Forum To submit a policy issue, visit sdsm.org.</td>
</tr>
<tr>
<td>2:30 pm</td>
<td>Policy Council Meeting</td>
</tr>
<tr>
<td>6 pm</td>
<td>Membership Mixer</td>
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<tr>
<td>7 pm</td>
<td>Awards Banquet, Scholarship Recognition &amp; Presidential Inauguration</td>
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<tr>
<td>9 pm</td>
<td>Dessert Reception</td>
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Maternal mortality has been in the news lately, and rightfully so. A recent USA Today article noted that approximately 700 women in this country die each year of pregnancy-related causes, making the U.S. “the most dangerous place to give birth in the developed world.” Indeed, the U.S. is the only industrialized country in which maternal deaths have been on the rise, growing by 26.6 percent from 2000 to 2014 (Figure 1), and it already has the dubious distinction of having the highest maternal mortality rate among wealthy nations. It is estimated that 60 percent of maternal deaths are preventable. For every maternal death, it is estimated that there are 50 to 100 women who experience a near-death event or severe morbidity.

One of the difficulties in addressing maternal mortality has been a lack of data on the topic. Most industrialized countries have a standardized method of tracking and analyzing maternal deaths in order to implement improved practices. However, the U.S. only began to record pregnancy status on its standard death certificates in 2003, and states were slow to adopt this. For purposes of data-tracking, a pregnancy-associated death is the death of a woman during or within one year of a pregnancy, regardless of the pregnancy outcome. A pregnancy-associated death may be pregnancy-related (caused by the pregnancy or delivery or a previous condition exacerbated by pregnancy), or it may be pregnancy-unrelated, e.g., a pregnant woman who dies in a natural disaster. In initially analyzing the data as tracking improved, it appeared that maternal mortality had doubled from 2000-2014; however, after controlling for the changes in data collection, a 26.6 percent rise in mortality was determined to be a more accurate calculation. The important message is that more women in the U.S. are dying during or in the year following a pregnancy, when those numbers are going down in every other industrialized country.

The most common causes of pregnancy-related deaths are cardiovascular disease, non-cardiovascular disease, infection/sepsis, hemorrhage, cardiomypathy, pulmonary embolism, cerebrovascular accident, hypertensive disorders of pregnancy, amniotic fluid embolism, and anesthesia complications. For many states, suicide is a leading cause of late maternal death (43 days to one year following pregnancy).

South Dakota is one of only four states that don’t have a maternal mortality review committee or at least have one currently in the process of being initiated. As a low population, rural state with some of the most pronounced areas of poverty in the country, South Dakota faces unique challenges related to both tracking and reducing maternal mortality. Because maternal mortality is listed as maternal deaths per 100,000 live births, a small change in absolute numbers can result in what appears to be a wide variation from year to year in overall mortality. South Dakota’s maternal mortality rate is listed at 24.5 per 100,000 by 2012-2016 data.
according to USA Today. The United Health Foundation’s website, America’s Health Rankings, lists South Dakota’s pregnancy-related mortality for 2016 at 28 deaths per 100,000 births. Our wide and sparsely populated geography makes access to care challenging, and patient transport can often be hindered by our notoriously unpredictable weather. Rural women are more likely to live a long distance from a hospital providing obstetrical care, and they tend to initiate prenatal care later in their pregnancies.

Additionally, large racial inequities exist in maternal mortality, independent of education and socioeconomic status. The overall estimated maternal mortality rate in the U.S. as of 2014 is 18 deaths per 100,000 live births. Broken down by race, the rate is 40 per 100,000 live births for black women, and 12.4 per 100,000 for white women. A black woman in the U.S. is four times more likely to die in a manner related to pregnancy and childbirth, even when controlling for education, socioeconomic factors, and pre-pregnancy medical conditions. While data collection on maternal deaths for black women is dismal, there is even less information available on maternal morbidity and mortality for Native American women. What data is available suggests that Native women are also at a higher risk of pregnancy-related mortality than white women, though not quite to the degree of black women.

So where is the silver lining?

The attention on maternal mortality has resulted in some encouraging changes. California recognized its own rising maternal mortality far before the rest of the country caught on. The California pregnancy-associated mortality review committee (CA-PAMR) was established in 2006. By studying maternal deaths across the state and implementing voluntary safety bundles, the state saw a 55 percent decline in maternal mortality between 2006 and 2013. Following the establishment of maternal mortality review committees, other states have followed suit, establishing safety bundles for obstetrical hemorrhage, increasing awareness of mental health and opioid use disorder and suicidality in the year following pregnancy, increasing access to mental health services, establishing simulation training for obstetrical emergencies, and improving access to long-acting reversible contraception to safely space pregnancies, among many other actions.

What is a maternal mortality review committee? A maternal mortality review committee (MMRC) is a multidisciplinary committee that reviews cases of maternal deaths within one year of pregnancy. Some states have expanded this to include severe morbidity or near-misses. The committee is made up of representation from multiple areas including public health, obstetrics and gynecology, maternal-fetal-medicine, family medicine, midwifery, nursing, forensic pathology, and behavioral and mental health. The resulting data provides a deeper understanding of circumstances surrounding maternal deaths and develops actionable recommendations to prevent future deaths. An MMRC must remain confidential and dedicated to a culture of promoting safety, not assigning blame. It examines both medical and non-medical causes of death, including such issues as suicide, domestic violence, drug overdose, and traffic fatalities. To be effective, an MMRC must have established protections and authority, including confidentiality of data and proceedings of the committee, authority to access hospital and law enforcement records, immunity for committee members, and regular reporting and dissemination of findings. Guidance on the establishment of an MMRC is available at ReviewToAction.org, a website established by the CDC in conjunction with the Association of Maternal and Child Health Programs.

The establishment of an MMRC has two immediate benefits:

1. The data collected by MMRC’s can be voluntarily shared with a national databank called the Maternal Mortality Review Information Application (MMRIA), sponsored by the CDC. MMRIA will act as a long-term repository for data and allow state committees to communicate in a common language and collaborate in case reviews and analyses.

2. States with an MMRC may participate in the Alliance for Innovation in Maternal Health (AIM), established by the Council on Patient Safety in Women’s Health, which provides implementation and data support for evidence-based patient safety bundles and tools.

Currently, 37 states and two cities have MMRCs. In November of 2018, the South Dakota State Medical Association passed a statement in support of the development of an MMRC in our state. In December of 2018, Congress passed and the president signed into law the Preventing Maternal Deaths Act, establishing federal funding for state MMRCs. Further federal legislation in support of studying and preventing maternal morbidity
and mortality is anticipated in the coming year and will likely build on the work of MMRCs, which makes it critical that one be established in our state.

Despite the delay in establishing an MMRC, South Dakota is starting to make some other positive changes. Several physicians in South Dakota and North Dakota have joined together with the March of Dimes to establish the North Dakota/South Dakota Perinatal Quality Committee (PQC). This committee, entirely voluntary and currently without funding, is dedicated to improving perinatal care throughout North Dakota and South Dakota. The work of an MMRC would be instrumental to informing the work of the PQC with regard to establishing and sharing safety bundles and best practices as they relate directly to maternal morbidity and mortality in our state. The state Department of Health has convened a Preventable Deaths Committee, a good start in exploring preventable deaths in South Dakota overall, and possibly a committee that may lay the foundation for an MMRC.

Maternal mortality is just the tip of the iceberg when we consider how one maternal death can ripple, affecting children, orphaned or left with a bereaved single-parent, as well as other family, friends, and communities. And healthcare workers are often secondary victims as well, grieving and struggling to understand why a seemingly healthy patient was lost around what should have been a joyous event. Now is the time to come together as a medical community, a state, and a nation in order to reverse this critical trend.

**RESOURCES**

12. Pregnancy maternal mortality surveillance system.

Don’t forget to send in your favorite scenic photo for South Dakota Medicine front cover consideration.

Send photos to ereiss@sdsmra.org.
Fact:

- A single JUUL pod contains as much nicotine as a pack of 20 regular cigarettes.
- Nicotine can harm a growing brain – it is known to damage brain circuits that control attention, learning, and susceptibility to addiction.
- Young people who use e-cigarettes may be more likely to go on to use regular cigarettes.

JUULing is dangerous.

The newest e-cigarettes are shaped like flash drives and are being used at alarming rates by teens. They are very discrete and come in an array of tasty flavors. Remind young patients and parents that tobacco use in ALL forms comes with serious health risks and encourage them to talk about JUULing.

Mom, everybody is JUULing. It’s no big deal... way safer than smoking, and it’s fun.

Well... some people use vape short term to help them quit smoking, but the truth is, vape is full of cancer causing chemicals, heavy metals, tin, lead, and high levels of nicotine. Not only is nicotine very addictive, but it can stunt your brain growth.

Some don’t contain nicotine. It’s just harmless flavor and water vapor...

A few maybe. But most kids want the nicotine buzz and all JUUL pods contain lots of nicotine. And it’s not fully regulated yet, so you may not know what you’re getting. If you keep using it, it will damage your brain. You’ll never you could’ve

Whoo – I didn’t know that. I think I might stay away from that stuff. So not worth it.

WARNING: E-cigarette use among young people has risen significantly over the last 5 years. Use among middle and high school students has now surpassed use of regular cigarettes.
Squamous Papilloma After Endoscopic Ablation of Barrett’s Esophagus: A Case Report And Review of Literature

By Mohamed A. Abdallah, MD; Muslim Atiq, MD; Jeffrey A. Murray, MD; and Bhareshkumar J. Patel, MD

Introduction

Squamous papilloma of the esophagus is a rare benign epithelial lesion that can be found incidentally during esophagogastroduodenoscopy (EGD). Incidence ranges from 0.01 to 0.45 percent in patients undergoing upper endoscopy, and a prevalence of 0.005 to 0.04 in the general population.1 The mean age of presentation is 51.5 years and male-to-female ratio ranges from 1.8 to 3.4.2 Lesions are solitary in 85 percent of patients.3 Seventy percent of lesions occur in the lower third of esophagus. On endoscopy, they appear as small, whitish-pink, wart-like exophytic projections.3,5

Histologically, lesions can be classified into three types: exophytic in 50 percent of patients; endophytic in 37 percent and spiked in 13 percent based on the predominant shape of the squamous papillae.5

Patients are usually asymptomatic. In symptomatic patients, epigastric pain is the chief complaint. Dysphagia can occur in patients with large lesions.1 Here we report the first case of squamous papilloma of the esophagus developing in a new mucosa after successful endoscopic ablation for short segment Barrett’s esophagus of the lower distal third of esophagus.

Case Report

A 58-year-old male patient has a past medical history of laparoscopic Nissen fundoplication, reflux esophagitis and a biopsy proven short segment Barrett’s esophagus (BE) diagnosed in 2009, with no evidence of dysplasia. Decision was to undergo endoscopic surveillance with biopsies every three years to five years after discussion with the patient. The patient had a surveillance EGD after three years which showed similar findings with no dysplasia. The patient had a low risk for development of esophageal carcinoma. Given his risk factors and the absence of dysplasia, the patient was interested in having endoscopic ablation of BE to further lower his risk for esophageal carcinoma. After discussing risks and benefits with the patient, a joint decision to undergo endoscopic ablation of his BE segment was reached.

The patient had an EGD by an experienced gastroenterologist, with circumferential radiofrequency ablation of BE using balloon-based endoscopic ablation system. This was followed by six endoscopic ablation procedures done in two- to three-month intervals over the following year. Complete eradication of intestinal metaplasia was successful and was confirmed with two subsequent EGD with biopsies that showed no evidence of Barrett’s esophagus.

The patient had a subsequent EGD demonstrating two nodules in the distal third of the esophagus (Figure 1). The first lesion was a 12 mm mucosal nodule and the second was a 6 mm mucosal nodule located at 34 cm and 36 cm from incisors, respectively (Figure 1). No biopsies were taken. After EGD, a thorough discussion with the patient about risks and benefits was done and a decision to pursue endoscopic ultrasonography (EUS) to better characterize the lesion and nearby structures was reached.

EUS examination was done in the following day. The two masses showed isoechoic character, with well-defined endosonographic borders with no evidence of lymph node enlargement or invasion of nearby structures. Complete resection of both nodules was done with band endoscopic mucosal resection (EMR) with band Ligator was performed for the 12 mm nodule, and resection with hot snare for the 6 mm nodule (Figure 2). Retrieved tissue was sent for pathology.

Biopsies of both nodules came back positive for squamous papilloma with no evidence of dysplasia or cancer.

Discussion

The exact etiology of esophageal papilloma is not clear.
However, inflammation driven pathogenesis is supported by the association of esophageal papilloma with reflux, esophagitis, mucosal irritation (for example, irritation from caustic agents, esophageal dilatation, nasogastric tubes) and location of lesions in the lower third of esophagus.1

Human papillomavirus (HPV), especially serotypes 6 and 11 have been associated with esophageal papillomatosis in many case reports. In one case series, 50 percent of the papillomas tested were positive for human papilloma virus, most commonly type 16, less often type 16 and 18 together.5 However, conflicting results from different studies don’t support this claim. Studies reported HPV prevalence ranging from less than 5 percent to about 50 percent in some studies, with wide variation in methods of detection and serotypes detected making clinicopathological association less clear.6 Evidence of causality of HPV for esophageal squamous cell carcinoma and malignant transformation induced by HPV has not been reported as well.5,7

Association of esophageal papilloma with many syndromes that have skin manifestations is known. Goltz syndrome, a congenital disorder of focal dermal hypoplasia that features hyperpigmentation, sclerodactyly, dysplastic changes of the teeth and bones, and perianal, oroesophageal, and genital papillomas has been associated with esophageal papilloma. Associations with other skin manifestations such as Tylosis, acanthosis nigricans is seen as well.9

A multifactorial etiology with the synergistic action of mucosal irritation, HPV infection in some patients and genetic factors is plausible as well.5,4 In our patient, literature review could not identify previous cases of esophageal papilloma.
papilloma occurring following endoscopic ablation of BE. In addition to that, our patient did not have any of the skin manifestations or other manifestations of the syndromes associated with esophageal papilloma. In addition to that, HPV testing was not performed given the conflicting results reported by various studies.

The possibility of contribution of inflammation from the previous history of Barrett’s esophagus to the development of esophageal papilloma in our patient is highly unlikely. The patient had complete eradication of Barrett’s esophagus that was confirmed by biopsies in two subsequent EGDs. The patient was on proton pump inhibitor (PPI) therapy, making the development of inflammation on the new mucosa after successful endoscopic ablation less likely as well.

Regarding management of squamous papilloma in the esophagus, endoscopic resection is indicated to differentiate esophageal papilloma from other similar appearing lesions: verrucous squamous cell carcinoma, granulation tissue, and papillary leukoplakia. Lesions smaller than 1 cm can usually be removed with a cold forceps biopsy, but larger lesions require endoscopic mucosal resection. Outcomes were excellent using this approach with resolution of the lesions, and no or low risk for recurrence. Based on the benign nature of this condition and the excellent outcome of resection, no follow up plans were made for this patient.

REFERENCES


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Giant Tubulopapillary Apocrine Cystadenoma with Mucinous Metaplasia

By Anna B. Bahnson, MD; B. Joel Tjarks, MD; and Amy M. Kerkvliet, MD

Introduction

In benign skin, mucinous metaplasia of apocrine and eccrine glands is a fairly well described, albeit uncommon, phenomenon. When it does occur, specific anatomic sites are usually involved (palms and soles, genitalia, etc.). The metaplasia is frequently attributed to chronic irritation, inflammation, or trauma. Mucin is normally not a product of mature keratinocytes. Studies of isolation and clonal analysis of human epidermal keratinocyte stem cells in long-term culture showed the presence of bipotent progenitors with the ability to produce both keratinocytes and mucin producing cells when under the influence of environmental factors. Mucinous metaplasia is defined as the presence of mucinous cells with a bluish, granular cytoplasm, akin to goblet cells interspersed with typical epithelial cells of the secretory portion of the apocrine glands. Case reports of hidradenoma, hidrocystoma, and invasive and in situ squamous cell carcinoma with mucinous metaplasia have all been reported. The most common lesion with mucinous metaplasia in the skin is mucinous syringometaplasia. Mucinous syringometaplasia is a rare condition that presents with a verrucous nodule on the soles or palms. It is characterized by an epidermal invagination, lined by nonkeratinizing squamous epithelium intermixed with mucin-containing cells. Rarely, mucinous metaplasia has been described within an apocrine cystadenoma. We present a case of a tubulopapillary apocrine cystadenoma with mucinous metaplasia arising on the scalp of a 32-year-old male.

Case Report

A 32-year-old male presented to a rural general surgery clinic with a slowly growing 3.5 cm scalp mass. Eight months prior to this visit, a fine-needle aspiration was performed on the mass revealing benign cyst contents composed predominantly of macrophages, cyst fluid, and rare columnar epithelial cells. The mass was excised to reveal a cystically dilated neoplasm with focal papillary projections with frond-like architecture and multiple gland-forming spaces in a hyalinized background (Figure 1). The cyst had a double-layer epithelial lining composed of cuboidal basal cells with round, regular nuclei and luminal variably cuboidal, columnar, and mucin-producing goblet cells (Figures 2-3). The goblet cells were highlighted by periodic acid Schiff (not shown) and mucicarmine (Figure 4) special stain. In other areas there were...
traditional features of an apocrine cystadenoma with luminal columnar cells with decapitation secretion (Figure 5). The basilar cells were positive for p63 and focally positive for S100 (not shown). The lesion was diagnosed as a tubulopapillary apocrine cystadenoma with mucinous metaplasia.

Discussion

The clinical differential diagnosis included epidermoid cyst, sebaceous cyst, pilar cyst, and benign lipoma with the most common cyst of the scalp being the pilar cyst. The pathologic differential diagnosis for this neoplasm included syringocystadenoma papilliferum and hidradenoma papilliferum.

Syringocystadenoma papilliferum is a benign adnexal neoplasm that occurs with equal frequency in both sexes. It occurs most commonly in childhood or adolescence and can be present from birth. They may grow in size during puberty and may multiply in number over time. Most syringocystadenomas occur on the head and neck and most often present as verrucous papules. They may also present in a linear array or as a solitary grey or red plaque. Those on the scalp are often alopecic. Pathologically, syringocystadenoma is distinctive for its wide papillary fronds continuous with the surface epithelium. The fronds are lined by a bilayer, with basal cuboidal cells and apical columnar apocrine cells. The cores of the fronds almost always contain a dense infiltrate of lymphocytes and plasma cells. Apocrine cystadenomas lack the plasma cell infiltrate (Figure 4) and typically lack epidermal connection of syringocystadenoma papilliferum.

Hidradenoma papilliferum is a benign papillary and cystic neoplasm that most commonly develops in the vulval and perianal regions of middle-aged women. The lesion most frequently presents as a slow-growing asymptomatic skin-colored dermal nodule, papule, or polypoid exophytic lesion that can ulcerate and bleed. Pathologically, hidradenoma papilliferum consists of a well-circumscribed nodule within the dermis. It typically lacks both a connection to the surface epithelium and dense plasmacytic infiltrate. Unlike apocrine cystadenomas, however, hidradenoma papilliferum typically has “maze-like” glandular spaces. Neither syringocystadenoma papilliferum nor hidradenoma papilliferum have been reported to demonstrate mucinous metaplasia.

Apocrine cystadenomas are on a spectrum of cystic lesions of the apocrine sweat glands which encompasses simple cysts such as hidrocystomas to cysts with more complex and solid components. The classic clinical presentations of these lesions is a blue, dome-shaped lesion on the face or periorbital region of an adult. Although the face is the most common site, involvement of the scalp, neck, trunk and genitals have been described. Although initially both apocrine and eccrine variants were described, it is now felt that most of these lesions are apocrine in nature. Apocrine cystadenomas are well circumscribed dermal or occasionally subcutaneous nodules that occasionally communicate with the epidermis. Papillary projections into the lumen of the cyst cavity, syncytial growth, and/or a tubular architecture are a typical feature of apocrine cystadenomas. They have a bilayer of epithelium with basal, p63 and SMA positive cells, and a luminal layer of columnar cells with...
decapitation secretion. Rarely, metaplastic phenomena with squamous or mucinous differentiation have been described. Typically, these cystic neoplasms range in size from 0.3 to 1.5 cm. Previously, the largest described case was one which measured 2 cm in greatest dimension. At 3.5 cm this is the largest apocrine cystadenoma reported to date. While the size of the tumor does not change its prognosis, the lesions may have a mass effect, especially when located around the soft tissues of the orbit.

**Conclusion**

This unique case has a number of unusual features which one may rarely encounter in apocrine cystadenomas, including mucinous metaplasia and large size. Our case adds to the current dearth of information regarding atypical presentations of these neoplasms and aids dermatologists and pathologists in correctly identifying an unfamiliar presentation of this cutaneous adnexal neoplasm.

**REFERENCES**


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A County-Level Health Index to Capture Geographic Variation in Health Conditions in North Dakota, South Dakota, and Minnesota

By Jing Zhao, PhD; Tess Weber, MPH; Jessica Hanson, PhD; Morgan Nelson, MS; Chad Birger, MS; and Susan Puumala, PhD

Abstract

Introduction: Individual health is influenced by multiple, potentially correlated factors including healthcare availability, community context, and socioeconomic factors. To measure the health changes at county-levels across North Dakota, South Dakota, and Minnesota, a measure of relative health, health index, was developed incorporating multiple indicators from domains of health conditions, health behaviors, and social determinants.

Methods: We combined data from all 206 counties in the aforementioned three states for the years 2008-2012 from multiple data sources. We performed factor analysis that accounted for a hierarchical structure of the overall health index comprising of 15 indicators.

Results: A hierarchical structure is identified in which three intermediate factors are connecting the health index with 15 health indicators. The grouping results of the 206 counties based on health index values demonstrate the existence of a gradient in health conditions in the Northern Plains.

Conclusions: The health status of urban areas was generally better than that of rural areas in the Northern Plains during this study period. The developed index adds stability to the estimates of the population characteristics, especially in rural, sparsely populated counties.

Introduction

It is well documented that individual health is influenced by multiple, potentially correlated factors that in-turn affect the health and well-being of a population. Among these are healthcare availability, community context, and socioeconomic factors. Addressing these social determinants of health is essential in achieving enhanced equity and reducing disparities in health outcomes.

Health disparities are defined as “differences in the incidence, prevalence, morbidity, mortality, and burden of disease and their adverse health conditions that exist among specific population groups.” Rural populations face unique health disparities such as higher rates of various preventable conditions including diabetes, cancer, and injuries. Rural residents also have higher rates of premature mortality and infant mortality, as well as higher death rates from unintentional injury, suicide, cardiovascular disease, cancer, and chronic obstructive pulmonary disease. Certain high-risk behaviors are likewise more prevalent in these communities, including smoking, obesity, physical inactivity, and poor diet. Many of these health outcomes and behaviors are correlated with socioeconomic issues, such as low income, less education, and unemployment. In addition, many rural populations have limited access to healthcare services.

Racial and ethnic minorities are also affected disproportionately by many negative health outcomes. American Indians (AIs) in particular have significant health disparities, including higher rates of mortality, chronic and infectious disease, smoking, lower education, unemployment and poverty. These disparities are especially pronounced in the Northern Plains. Cobb et al. found that Northern Plains AIs have higher rates of negative health behaviors.
compared to AIs nationwide, including obesity, heavy drinking, and smoking. These inequalities necessitate further research to understand the nature and scope of disparities in these disadvantaged populations.

The purpose of this study was to create a measure of relative health that could be applied at county-levels across three states in the Northern Plains of the U.S.: North Dakota, South Dakota, and Minnesota. This area is composed of 206 counties (66 counties in South Dakota, 53 counties in North Dakota, and 87 counties in Minnesota). Data used to construct this health index were taken from multiple data sources for the years 2008-2012, and 15 indicators were structured into three domains: health conditions and outcomes, health behaviors, and socioeconomic factors. See Table 1 for a list of the data sources and descriptive statistics for each of these variables. All but one (household income) of the 15 variables were proportions.

Three groups of indicators were chosen to be representative of health conditions and outcomes. The first group includes mortality rates from Centers for Disease Control and Prevention (CDC). The second group was related to chronic disease, also from the CDC, and consisted of

### Table 1. Data sources and descriptive statistics of the health indicators.

<table>
<thead>
<tr>
<th>Domains</th>
<th>Sub-domains</th>
<th>Indicators*</th>
<th>Data sources</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Outcomes</td>
<td>Mortality rate</td>
<td>Mortality</td>
<td>Centers for Disease Control and Prevention (<a href="https://wonder.cdc.gov">https://wonder.cdc.gov</a>)</td>
<td>0.0038</td>
<td>0.01040</td>
<td>0.024</td>
<td>0.023</td>
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<td></td>
<td>Chronic disease rates</td>
<td>Obesity</td>
<td>Centers for Disease Control and Prevention (<a href="http://www.cdc.gov/diabetes/atlas/countydata/atlas.html">http://www.cdc.gov/diabetes/atlas/countydata/atlas.html</a>)</td>
<td>0.2160</td>
<td>0.29200</td>
<td>0.441</td>
<td>0.2310</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
<td>Centers for Disease Control and Prevention (<a href="http://www.cdc.gov/diabetes/atlas/countydata/atlas.html">http://www.cdc.gov/diabetes/atlas/countydata/atlas.html</a>)</td>
<td>0.0560</td>
<td>0.07200</td>
<td>0.195</td>
<td>0.1450</td>
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<tr>
<td></td>
<td>Infectious disease rates</td>
<td>Chlamydia rate</td>
<td>Department of Health (<a href="http://doh.ad.gov/statistics/http://www.health.state.mn.us/divs/depc/diseases/hiv/statshttps://www.nidod.gov/">http://doh.ad.gov/statistics/http://www.health.state.mn.us/divs/depc/diseases/hiv/statshttps://www.nidod.gov/</a>)</td>
<td>0.0600</td>
<td>0.01153</td>
<td>0.193</td>
<td>0.1933</td>
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<td></td>
<td></td>
<td>Gonorrhea</td>
<td>Department of Health (<a href="http://doh.ad.gov/statistics/http://www.health.state.mn.us/divs/depc/diseases/hiv/statshttps://www.nidod.gov/">http://doh.ad.gov/statistics/http://www.health.state.mn.us/divs/depc/diseases/hiv/statshttps://www.nidod.gov/</a>)</td>
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<td>0.00010</td>
<td>0.046</td>
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<td></td>
<td></td>
<td>Tuberculosis</td>
<td>Department of Health (<a href="http://doh.ad.gov/statistics/http://www.health.state.mn.us/divs/depc/diseases/hiv/statshttps://www.nidod.gov/">http://doh.ad.gov/statistics/http://www.health.state.mn.us/divs/depc/diseases/hiv/statshttps://www.nidod.gov/</a>)</td>
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<td>0.00001</td>
<td>0.008</td>
<td>0.0088</td>
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<td>Health Behaviors</td>
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<td>Smoking</td>
<td>Cigarette smoking prevalence in US counties: 1996-2012 (<a href="http://www.cdc.gov/cancer/statfacts/pdf/fact_sheet.pdf">http://www.cdc.gov/cancer/statfacts/pdf/fact_sheet.pdf</a>)</td>
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<td>0.22700</td>
<td>0.380</td>
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<td>Alcohol use</td>
<td>Alcohol drinking</td>
<td>Institute for Health Metrics and Evaluation (<a href="http://www.healthdata.org/us-healthdata/download#S">http://www.healthdata.org/us-healthdata/download#S</a>)</td>
<td>0.2740</td>
<td>0.62700</td>
<td>0.722</td>
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<td></td>
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<td>Alcohol binge drinking</td>
<td>Institute for Health Metrics and Evaluation (<a href="http://www.healthdata.org/us-healthdata/download#S">http://www.healthdata.org/us-healthdata/download#S</a>)</td>
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<td>0.23800</td>
<td>0.348</td>
<td>0.1870</td>
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<tr>
<td></td>
<td>Inactivity</td>
<td>Inactivity</td>
<td>Centers for Disease Control and Prevention (<a href="http://www.cdc.gov/diabetes/atlas/countydata/atlas.html">http://www.cdc.gov/diabetes/atlas/countydata/atlas.html</a>)</td>
<td>0.1500</td>
<td>0.24100</td>
<td>0.386</td>
<td>0.2360</td>
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<tr>
<td>Socioeconomic Factors</td>
<td>Access to care</td>
<td>Primary care physician</td>
<td>American Medical Association (<a href="https://datawarehouse.hrsa.gov/">https://datawarehouse.hrsa.gov/</a>)</td>
<td>0.0060</td>
<td>0.00068</td>
<td>0.0049</td>
<td>0.0049</td>
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<td></td>
<td>Unemployment</td>
<td>Unemployment</td>
<td>Bureau of Labor Statistics (<a href="https://www.bls.gov/au">https://www.bls.gov/au</a>)</td>
<td>0.0110</td>
<td>0.05100</td>
<td>0.162</td>
<td>0.1510</td>
</tr>
<tr>
<td></td>
<td>Median household income*</td>
<td>Median household income*</td>
<td>U.S. Census Bureau, Small Area Income and Poverty Estimates (<a href="https://www.census.gov/did/www/saipe/data/index.html">https://www.census.gov/did/www/saipe/data/index.html</a>)</td>
<td>18600</td>
<td>45955</td>
<td>60324</td>
<td>67464</td>
</tr>
<tr>
<td></td>
<td>Poverty</td>
<td>Poverty</td>
<td>U.S. Census Bureau, Small Area Income and Poverty Estimates (<a href="https://www.census.gov/did/www/saipe/data/index.html">https://www.census.gov/did/www/saipe/data/index.html</a>)</td>
<td>0.0400</td>
<td>0.11600</td>
<td>0.620</td>
<td>0.5600</td>
</tr>
</tbody>
</table>

*All indicators are proportions, unless otherwise stated. "* is the median value of the combined incomes of all people sharing a particular household or place of residence."
obesity and diabetes rates. The third group was composed of infectious disease rates, including chlamydia, gonorrhea, and tuberculosis (TB) rates, from the departments of health of each state. Issues accounted for in the data set were smoothing for small counts and imputation for missing data.

To characterize health behaviors, data regarding the prevalence of smoking, alcohol use, and physical inactivity were obtained from Institute for Health Metrics and Evaluation and the CDC. Four indicators were selected to describe the socioeconomic conditions of the study area: access to care, unemployment, median household income, and poverty. The unemployed population encounters higher mortality rates and worse health conditions than the employed population. Income affects access to health care and healthy lifestyles. Percentage of the population in poverty was chosen since poverty is highly correlated with mortality, the prevalence of medical conditions, the incidence of disease, and poor health behaviors.

Constructing the Health Index
The health index was developed by factor analysis of the aforementioned 15 variables since we believed that there was a hierarchical structure to the overall index comprising of indicators from three related domains (health outcomes and conditions, health behaviors, and socio-economic conditions). Prior to index construction, preliminary steps were carried out to reduce bias. These included imputations for missing data and standardization of variables.

Two imputation methods were applied in this study to deal with missing data under different scenarios. Mean imputation was used for random missing values that did not have a specific pattern. Each missing observation was substituted with the mean of the adjacent non-missing observations for each particular variable. The other method was imputation using Bayesian spatial smoothing method, which was specifically applied to infectious disease rates which were sparse in areas with small populations. This imputation method estimated the spatial correlation for each infectious disease variable individually and used these spatial relationships to estimate all observations based on non-missing observations. A Bayesian spatial smoothing method was adopted here to help areas borrow information from neighboring areas and produce a more balanced estimation of disease rates and implemented through an R package “CARBayes.”

Because the indicators were retrieved from multiple sources and have different measurement units, standardization was applied to convert indicators to a common scale with mean zero and standard deviation of one before the construction of health index.

After the preliminary steps, the weights of each indicator in constructing the final health index were determined by exploratory factor analysis. First, the number of factors to extract in the factor analysis was determined by combining results from multiple functions provided in the R package “nFactors,” which included eigenvalues, parallel analysis, optimal coordinates, and acceleration factor. Then the exploratory factor analysis was performed on the standardized indicator data set using a built-in R function “factanal.” The approach used by Nicoletti et al. to assign weight to each indicator was adopted here. That is, the affiliating factor of each indicator was chosen to be the one corresponding to the largest squared factor loading. Then three intermediate composition indicators (ICIs) were constructed from the indicators associating with the three factors, with the weight of each indicator defined as the proportion of its squared factor loading to the sum of squared factor loadings of all indicators contained in this factor. Finally, the three intermediate composite indicators were aggregated by assigning a weight to each one of them equal to the proportion of the explained variance in the dataset.

Index Validity
The construct validity was tested to verify the association between the constructed index and county health rankings using Spearman’s correlation coefficient. The reliability was tested by Cronbach’s alpha coefficient to judge how the variables were internally consistent. The closer the coefficient was to one, the better the verification that the variables were homogeneous.

Results
Health Index
The health index was defined by the outputs of exploratory factor analysis, in which the first three factors explained 64 percent of the total variance of the model (Table 2a). The sufficiency of the decision that retaining three factors in this model was demonstrated in the scree plots (Figure 1), in which two criteria support this decision. The squared factor loadings of all variables in the three factors presented in Table 2b, which were generated with a “varimax” rotation in the model since it had more evenly spreading components than the unrotated scenario.
The hierarchical structure of the health index is presented in Figure 2, with the values on the arrows representing the assigned weights for all the variables and three factors. The composition of the health index from the three ICIs is demonstrated in the inner flow, with the weights of ICIs being 0.557, 0.245, and 0.198 respectively. The outer flow represents the portion of individual indicators contributed to its affiliated ICI. ICI 1 is composed of eight factors, which are alcohol drinking, median household income, uninsured, smoking, poverty, primary care provider, diabetes, and obesity, with weights ranging between 0.006 and 0.172. ICI 2 is formed by chlamydia, gonorrhea, and tuberculosis with evenly distributed weights (0.332, 0.394, and 0.273). The third ICI contains mortality, unemployment, inactivity, and binge drinking, where inactivity contributed most (0.359) and mortality contributed least (0.150). These ICIs do not necessarily have realistic meanings since they are transitional nodes to help split the variance of the data set in order to form the final index.

The distributions of the health index across the study area for years 2008-2012 are shown in Figure 3. Health indices in Minnesota are centered at around 0.2, while those in North Dakota and South Dakota are centered at about zero. In addition, the distributions in North Dakota and South Dakota are more spread out than in Minnesota and are skewed to the left. It is indicated from these plots that

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Factor Loadings</th>
<th>Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.031</td>
<td>0.150</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.634</td>
<td>0.136</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.770</td>
<td>0.167</td>
</tr>
<tr>
<td>Chlamydia rate</td>
<td>0.092</td>
<td>0.332</td>
</tr>
<tr>
<td>Gonorrhea rate</td>
<td>0.093</td>
<td>0.394</td>
</tr>
<tr>
<td>Tuberculosis rate</td>
<td>0.020</td>
<td>0.273</td>
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<tr>
<td>Smoking</td>
<td>0.727</td>
<td>0.158</td>
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<tr>
<td>Alcohol drinking</td>
<td>0.750</td>
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<td>Alcohol binge drinking</td>
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<td>0.203</td>
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<tr>
<td>Inactivity</td>
<td>0.325</td>
<td>0.359</td>
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<tr>
<td>Primary care physician</td>
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<td>0.006</td>
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<tr>
<td>Uninsured</td>
<td>0.419</td>
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<tr>
<td>Unemployment</td>
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<td>0.288</td>
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<tr>
<td>Median household income</td>
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</tr>
<tr>
<td>Poverty</td>
<td>0.808</td>
<td>0.173</td>
</tr>
</tbody>
</table>

*All factors represent the connection between variables and factors.*
the overall health status in MN is better than in SD and ND over the five-year period. Moreover, there are small portions in SD and ND living in much more disadvantaged situations. These findings give an overview of the health status at the state level, while the county-level examination provides more specific information.

All of the 206 counties within the study area are classified into four groups based on the quantiles of the health index. This grouping step could help eliminating the bias introduced in constructing the health index. Table 3 presents the mean values of the index and of the 15 variables by health index group for years 2008-2012. The first group is characterized by the highest mean index value with the lowest rates of obesity, diabetes, smoking, alcohol binge drinking, and inactivity, and with the highest rate of median household income over the five years. At the other end, the fourth group is characterized by the lowest mean health index and the lowest alcohol drinking and unemployment rates for most of the five years. The grouping of this county health index is displayed in the cartographic representation (Figure 4). Areas with the red border are American Indian reservations in the Northern Plains. The counties within group 1 are generally located at the lower right of the study area. These are principally counties with a relatively high population, easy access to health care, and more job opportunities. Conversely, the counties within groups 3 and 4 are located in rural areas with relatively low population and less health care facilities and job opportunities. It is worth noticing that many of these counties in groups 3 and 4 encompassed reservation communities.

Validity Test
Construct validity of the health index was tested by correlation coefficients with the Z score in Country
<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
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<td>0.011</td>
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<td>0.01</td>
<td>0.012</td>
<td>0.011</td>
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<td></td>
<td>0.01</td>
<td>0.01</td>
<td>0.012</td>
<td>0.011</td>
</tr>
<tr>
<td>Obesity</td>
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<td>0.287</td>
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<td></td>
<td>0.265</td>
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<td>0.289</td>
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<td>0.333</td>
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<td>Tuberculosis rate</td>
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<td></td>
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<td>0.624</td>
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<td>0.622</td>
<td>0.629</td>
<td>0.626</td>
<td>0.576</td>
</tr>
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</table>

Table 3. Summary of grouping results based on the constructed health index.
As shown in Table 4, the correlation coefficients were high or relatively high in these states, which indicated that the health index corresponded to Country Health Ranking. The high Cronbach’s coefficient among variables in each of the three ICIs (0.89 for ICI 1, 0.78 for ICI 2, and 0.58 for ICI 3) supported the hypothesis that these variables measure a three-factor concept health index.

Discussion

This paper presents a brief overview of the data and selected methods that were used to construct a composite index, which applied factor analysis using multidimensional health indicators. We demonstrated the processes of index development that ranged from data preprocessing to index formation, with special attention paid to the imputation method of missing values and the computation procedure using factor analysis.

Our composite health index was constructed with a factor analysis framework using data from multiple sources at the county level. Working at this resolution adds stability to the estimates of this population’s characteristics, especially in rural, sparsely populated counties, and may enhance the precision of the identification and measurement of health events observed. Our study complements earlier work by assigning weights to individual indicators and by retrieving weights from real data rather than using predetermined weights. Our findings are unique due to the granularity of our data, which allowed us to examine trends over five years.

Grouping counties based on the constructed health index also facilitates several important population health implications. These county-level health data allow for errors introduced in the modeling process, which results in broader applications than the absolute value of a health index. It also demonstrates the existence of a health condition gradient in South Dakota, ND, and MN.

Our study is consequential as it focuses on the northern plains states, a rural/remote geographic area with high numbers of AIs and also high health disparities among rural and reservation regions compared to more populated areas. For example, AIs in the northern plains continue to have extensive economic and health disparities, as well as vast differences in socioeconomic and behavioral determi-
nants. This inequity was also noted in our study, as reservation communities were often encompassed in groups 3 and 4.

The health status of urban areas was generally better than that of rural areas during this study period. Groups 3 and 4 were more concentrated on the western side of the study region in areas of lower population densities. This is consistent with previous research, as health disparities in rural settings are well documented. Contributing to these poor health outcomes are behavioral and socioeconomic factors, such as smoking, alcohol consumption, inactivity, unemployment, and low income, all of which were found to be more prevalent in groups 3 and 4. These observations indicate a possible application of this health index in studying and intervening in health disparities, particularly in rural and minority populations.

Our scale has also been shown to be robust using validity criterion and is consistent with county health rankings. This allows for replication in future years to show the temporal changes and thus has the potential to be an evaluation tool that reflects the impact of public health policy and other social intervention programs. In addition, there is a lack of measurements that weigh indicators based on their statistical association with the composite indicator being constructed in a county-level. The health index described in this study fills this gap with an application using data from the Northern Plains.

In addition, our health index is a measure of overall health which combines indicators data representing health outcomes, health behaviors, and socioeconomic factors. This definition allows the index to be implemented for both description and explanation. In a descriptive context, our index can be used in health planning or resource allocation. The index may also contribute to collaborations between local and regional policy makers and public health professionals to target sensitive populations and develop interventions and actions better adapted to the behavioral, socioeconomic factors specific to this setting. In an explanatory framework, our index can be used to investigate social or behavioral differences and health disparities.

This study has several limitations. First, because of the availability of data sources, only 15 variables were included in this study. Efforts have been made nationwide to collect data related to health outcomes and socioeconomic factors, which will allow us to expand the health index in the future. With more and more health indicators accessible, we will be able to create more robust health indices that could better reflect the health conditions and be more sensitive to changes in individual indicators. Moreover, our study presents the typical limitations of all such studies due to its geographical design. Because our index is an aggregated measure of health conditions constructed at the county level, the relations observed between variables may be different than on smaller geographic units such as census blocks or within individuals. However, given the rural nature of our region, models may become unstable for smaller geographic units.

Conclusion

In conclusion, this index is an innovative tool that allows for the detection of county-level health disparities. Our index may be used to assess changes over time within this area, thereby allowing for comparisons as policies and programs are implemented. We also envision the expansion of our health index model with available nationwide county-level data. Our index facilitates needs-based allocation of resources, which could substantially improve health outcomes of rural and native communities in the Northern Plains and elsewhere.

Acknowledgement: The authors would especially like to thank Drs. Amy Elliott and DenYelle Kenyon for their valuable suggestions in this study, as well as the CRCAIH team who commented on this study during group discussions.

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Development of Leiomyosarcoma in a Patient Treated with Azathioprine

By Mohamed Abdallah, MBBS; Mohamed Saleh, MD; Hesham Elgouhari, MD; and Mark K. Huntington, MD, PhD

Abstract
Cirrhosis resulting from autoimmune hepatitis is associated with an increased risk of hepatocellular carcinoma. A common treatment for autoimmune hepatitis, azathioprine, is also associated with the development of many other cancers, predominantly lymphomas. The strongest association is seen for post-transplant lymphoma and hepatosplenic T-cell lymphoma in Crohn's disease and ulcerative colitis patients; there is also an association with a variety of cutaneous malignancies. A relationship between azathioprine and sarcoma has not been demonstrated, though there have been sporadic case reports. We report here the development of leiomyosarcoma in a patient who was treated with azathioprine for autoimmune hepatitis without cirrhosis.

Introduction
Azathioprine is an immunosuppressive drug that is used in the treatment of many conditions including renal transplantation, rheumatoid arthritis, inflammatory bowel disease, and autoimmune hepatitis.1-5 Despite its efficacy in treatment of such conditions, azathioprine comes with its side effects, too.

The principal side effect of azathioprine is dose-related bone marrow suppression, but it may also cause occasional liver impairment and cholestatic jaundice; hepatic veno-occlusive disease has been reported. In addition, a number of hypersensitivity reactions, usually manifesting as a rash, have been reported.6

Perhaps the most significant risk, as with many immunosuppressant agents, is the development of cancer. Many malignancies have been associated with the azathioprine therapy. The strongest association is seen for lymphomas, urinary tumors, and cutaneous malignancies.7-14 We report here a case of leiomyosarcoma occurring in a patient whose autoimmune hepatitis (AIH) was treated with azathioprine.

The risk of soft tissue sarcoma in AIH patients is extremely low, with only one reported case (angiosarcoma) found in the literature.15 However, when AIH results in cirrhosis, it is associated with 1.1 percent per year risk of hepatocellular carcinoma (HCC). Routine surveillance for HCC has been recommended in AIH patients with cirrhosis who would be candidates for curative interventions should it be found.16

Case Report
The patient is a 52-year-old female with a nine-year history of autoimmune hepatitis, which was under good control on prednisone 10 mg daily and azathioprine 50 mg twice daily. The patient was followed regularly by her gastroenterologist. A liver mass was found on routine ultrasound screening for HCC; at the time she was completely asymptomatic. Magnetic resonance imaging (MRI) was done and showed that there were multiple lesions in the liver and the lungs (Figure 1).

Preliminary pathological evaluation of a biopsy of one of the liver lesion provided the diagnosis of high-grade soft tissue sarcoma with features consistent with leiomyosarcoma (Figure 2). This was in contrast to the HCC for which the screening was performed. As this is an unusual liver tumor, a section was sent to a consulting pathology laboratory specializing in rare tumors. The diagnosis of a leiomyosarcoma was confirmed and it was suggested that the tumor represented metastatic disease as primary liver leiomyosarcoma is extraordinarily rare. The patient was transferred
to a quaternary referral center; positron emission tomography (PET-CT) showed multiple sites of disease including liver, lung, mediastinum, peritoneum, bone, and mesentery (Figure 3).

Azathioprine was stopped and treatment with anthracycline base chemotherapy along with olaratumab was initiated. She was given olaratumab 15 mg/kg IV on days one and eight every three weeks, along with liposomal doxorubicin 37.5 mg/m² on day one of each three-week cycle for eight cycles, after which the olaratumab was continued as monotherapy. Following eight cycles of therapy, repeat PET-CT showed continued progression of the disease with increase in the lesion size. Her regimen was changed from olaratumab to gemcitabine 800mg/m² on days one and eight of the three-week cycle, but the disease continued to progress. The patient was ultimately admitted to hospice.

**Discussion**

The risk of developing malignancy in AIH patients is elevated, especially for oro-pharyngeal and hepatobiliary tumors. This risk is almost exclusively associated with the presence of cirrhosis; for example, in the absence of cirrhosis, HCC does not occur. Given this patient’s lack of cirrhosis, we believe the AIH was not the cause of her tumor.

Many malignancies have been associated with the azathioprine therapy. It has been primarily associated with lymphomas, urinary tract, and cutaneous malignancies, but HCC and sarcoma have also been reported.

A search of the PubMed database for azathioprine AND

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![Figure 1. MRI demonstrating examples of the patient’s tumors in the liver (arrow, left) and lung (arrow, right). Multiple tumors were seen in different slices.](image)

![Figure 2. Histological sections of the tumor (A) juxtaposed with normal liver tissue (B), H&E (left) and actin-immunostaining (right)](image)
leiom yosarcoma. Kaposi sarcoma in HIV-negative patients have been reported. 23-25 In two cases of Kaposi sarcoma in HIV-negative IBD patients on azathioprine, 23,25 there was reported regression of sarcoma after discontinuation of azathioprine. Kaposi sarcoma arising in a patient with azathioprine treatment for bullous pemphigoid also regressed after stopping azathioprine. 24 Similar was a case of biopsy-proven soft tissue sarcoma that metastasized to the chest wall and lung in an 85-year-old female with rheumatoid arthritis. The lesions were considered inoperable and the focus of care became palliative; the sarcoma resolved one year after discontinuation of azathioprine. 26 Pleomorphic liposarcoma that developed in the chest wall of a patient treated with azathioprine for Crohn’s disease was successfully treated with surgery and radiotherapy following discontinuation of azathioprine. 27 Unfortunately, neither withdrawal of azathioprine nor aggressive treatment was successful in treating our patient’s sarcoma.

Soft tissue sarcomas (STS) are a rare and heterogeneous group of tumors of mesenchymal origin, which includes more than 100 different histologic subtypes. They represent less than 1 percent of all adult malignancies. 28 They are usually localized on diagnosis. However, when they present with distant metastasis, lungs are involved in more than 80 percent of cases. 29 STS staging with tumor, node, metastasis (TNM) system is usually used. However, a validated nomogram developed by Memorial Sloan-Kettering Cancer Center is available online to aid in predicting survival and treatment decision-making for individual patients (www.mskcc.org/nomograms/sarcoma/post_op). 30

Surgical resection can be curative in patients with isolated pulmonary metastatic disease. However, for patients with advanced unresectable STS, offering participation in ongoing clinical trials can be reasonable for appropriate candidates. If that is not feasible, treatment with doxorubicin and olaratumab is preferable to other regimens. 31,32 For patients with progression on olaratumab plus doxorubicin, trabectedin, eribulin, pazopanib, pegylated liposomal doxorubicin, an ifosfamide-containing regimen, gemcitabine, or gemcitabine/docetaxel are second line treatments that showed success in selected patients. 33-36

Conclusion

We report here the first – to our knowledge – case of leiom yosarcoma associated with azathioprine treatment. This expands the variety of malignancies potentially associated with this specific immunosuppressive therapy.

Acknowledgment: The authors wish to thank Dr. Karla Murphy of Physicians Laboratory, Sioux Falls, South Dakota, for the images of the patient’s histopathology reproduced here.

REFERENCES


Please note: Due to limited space, we are unable to list all references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

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Pulmonary Hypertension: Brief Review Article

By Ahmed Gohar, MD; Anup Shrestha, MD; and Adam Stys, MD

Abstract

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (mPAP) 25 mmHg or greater at rest; this measurement is obtained during right heart catheterization. The exact prevalence of PH in the U.S. is unknown. Advances in hemodynamic studies of the right heart side and pulmonary circulations has helped improve our understanding of this condition. This better understanding aids the development of treatment agents aimed at improving quality of life, morbidity and mortality. Awareness of this condition and understanding the classification of PH and the available treatment modalities is crucial hence we aim to briefly review the classification, diagnosis and treatment of PH in this article.

Introduction

Our understanding of PH has developed over the past decades evolving from postmortem autopsy observations, through the advent of right heart catheterization with in-depth hemodynamic studies and to understanding the molecular basis and genetics. Pulmonary hypertension, a once ambiguous entity that was labeled as “the kingdom of the near dead” due to associated mortality, is now more understood and is targeted for ongoing research for further understanding of the disease that can potentially offer new treatments to improve outcomes.\(^1\)PH is defined as mean pulmonary artery pressure (mPAP) 25 mmHg or greater at rest; this measurement is obtained during right heart catheterization.\(^1\) This article aims to briefly review classification, diagnosis and treatment of PH.

Classification

The current classification of PH is the result of five meetings by the world health organizations (WHO) on pulmonary hypertension. The first world symposium on PH (WSPH) was held in 1997, it was prompted by an epidemic of pulmonary hypertension attributed to the use of aminorex, an appetite suppressant used in Europe between 1965 and 1968.\(^4\) The first WSPH classified PH as either primary or secondary.\(^3\) Currently PH is classified into five main groups listed in Table 1.\(^6\) This classification is guided by shared pathological, clinical and management features. The importance of identifying which group of PH is the culprit is important as pulmonary artery hypertension (PAH) specific treatment agents could have deleterious effects on other groups like PH due to left heart disease (group 2).

Pulmonary Artery Hypertension (Group 1)

Pulmonary artery hypertension (PAH) refers to a sub-group of PH that is characterized by elevated mPAP 25 mmHg or greater at rest, pulmonary artery wedge pressure (PAWP) 15 mmHg or fewer and increased pulmonary vascular resistance (PVR) greater than 3 wood units.\(^2\) PAH is believed to be the result of sustained vasoconstriction, arterial vascular remodeling and in situ thrombosis, these processes are driven by multiple factors including imbalance between vasoconstrictor and vasodilator mediators, inflammation and altered apoptosis.\(^7\) Pulmonary venous remodeling was also identified in some subcategories of PAH such as scleroderma-associated PAH.\(^3\) PAH is further divided into idiopathic PAH (IPAH) where there is no clear cause for the PAH, heritable where multiple mutations have been identified and PAH in association with other conditions (Table 1).\(^6\) Other related entities are pulmonary veno-occlusive disease (PVOD) which is now designated as 1', and
persistent neonatal pulmonary HTN which is designated as 1" and is more pertinent to the pediatric population. PVOD represents a challenge as it can be misdiagnosed as IPAH, a helpful clue could be the presence of ground glass opacities and interlobular thickening on imaging which are absent with IPAH. While PVOD may have some response to IPAH-targeted medical therapy, there is a high rate of pulmonary edema and even death associated with the use of such treatment so proper identification of PVOD would allow careful monitoring, slow titration of doses and concomitant use of diuretics when such treatments are used. Currently the definitive treatment for PVOD is lung transplantation.

### Table 1. Classification of PH, adapted from guidelines of the 5th World Symposium held in Nice, France, 2013.

<table>
<thead>
<tr>
<th>Classification of PH</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td>1 Pulmonary arterial hypertension</td>
<td>1.1 Idiopathic&lt;br&gt;1.2 Heritable&lt;br&gt;1.2.1 BMPR2&lt;br&gt;1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3&lt;br&gt;1.2.3 Unknown&lt;br&gt;1.3 Drugs and toxins induced&lt;br&gt;1.4 Associated with:&lt;br&gt;1.4.1 Connective tissue diseases&lt;br&gt;1.4.2 HIV infection&lt;br&gt;1.4.3 Portal hypertension&lt;br&gt;1.4.4 Congenital heart disease&lt;br&gt;1.4.5 Schistosomiasis&lt;br&gt;1.5 Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</td>
<td>1' Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>2 Pulmonary hypertension due to left heart disease</td>
<td>2.1 Systolic dysfunction&lt;br&gt;2.2 Diastolic dysfunction&lt;br&gt;2.3 Valvular disease&lt;br&gt;2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
</tr>
<tr>
<td>3 Pulmonary hypertension due to lung diseases and/or hypoxia</td>
<td>3.1 Chronic obstructive pulmonary disease&lt;br&gt;3.2 Interstitial lung disease&lt;br&gt;3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern&lt;br&gt;3.4 Sleep-disordered breathing&lt;br&gt;3.5 Alveolar hypoventilation disorders&lt;br&gt;3.6 Chronic exposure to high altitude&lt;br&gt;3.7 Developmental lung disease</td>
</tr>
<tr>
<td>4 Chronic thromboembolic pulmonary hypertension</td>
<td>4.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy&lt;br&gt;4.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis&lt;br&gt;4.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders&lt;br&gt;4.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH</td>
</tr>
</tbody>
</table>

BMPR: bone morphogenic protein receptor type II; CAV1: caveolin-1; ENG: endoglin; HIV: human immunodeficiency virus; ALK1: activin receptor-like kinase; SMAD9: mothers against decapentaplegic homolog 9; KCNK3: potassium channel subfamily K member 3
Pulmonary Hypertension Due to Left Heart Disease (Group 2)

Left heart disease (LHD) is a very common cause of PH especially in the setting of heart failure both with reduced and preserved ejection fraction. Despite that, the actual prevalence of PH-LHD is unclear. PH-LHD is classically identified as mPAP 25 mmHg or greater and DPD less than 7 mmHg in the presence of elevated left heart filling pressures denoted by a pulmonary capillary wedge pressure (PCWP) greater than 15 mmHg. The intuitive thought is that this group of PH is due to the passive consequences of increased left heart side filling pressures. Hence at least the initial vascular remodeling and pulmonary vascular disease. \(^{17-20}\)

P H is due to the passive consequences of increased left heart filling pressures. \(^{22}\)

Combined post capillary and precapillary PH (with PAWP greater than 15 mmHg and DPD less than 7 mmHg), and severe PH-LHD with mPAP 35 or greater \(^{22}\)

It is thought that chronically elevated PAWP, the resultant pulsatile load and other factors lead to a response in the precapillary part of the pulmonary circulation in the form of vasoconstriction, decreased nitric oxide, decreased response to vasodilators and in some instances precapillary vascular remodeling and pulmonary vascular disease. \(^{18-20}\)

Guided by current evidence, the last WSPH has identified diastolic pressure difference (diastolic PAP – mean PAWP) 7 mmHg or greater as a tool to identify the additional presence of a precapillary component versus merely passive PH. \(^{21,22}\)

The use of diastolic pressure difference (DPD) over transpulmonary pressure gradient (mPAP – PCWP) is preferred as DPD is less influenced by stroke volume, and PAWP. \(^{21}\)

Currently PH-LHD is further classified into isolated post capillary PH (with PAWP greater than 15 mmHg and DPD less than 7 mmHg), and combined post capillary and precapillary PH (with PAWP greater than 15 mmHg and DPD 7 mmHg and greater). \(^{21}\)

Making this differentiation may have implications on treatment in the future.

Pulmonary Hypertension Due to Chronic Lung Disease and/or Hypoxia (Group 3)

PH is a common complication of chronic lung disease (CLD). It can occur in the setting of multiple lung disorders including chronic obstructive lung disease (COPD), diffuse parenchymal lung disease/idiopathic pulmonary fibrosis DPLD/IPF, combined pulmonary fibrosis and emphysema (CPFE), sleep related breathing disorders and high-altitude related hypoxemia. \(^{21,28}\)

There are multiple involved mechanisms, hypoxia induced vasoconstriction is a primary mechanism that is physiologically meant to divert perfusion from poorly ventilated areas of the lungs to normoxic areas maximizing gas exchange. \(^{29,30}\)

In chronic hypoxia and with increased severity of pulmonary disease this vasoconstrictive response can lead to elevated PAP and PH. \(^{30,31}\)

Other involved factors are chronic hypoxia-related inflammation and vascular remodeling. \(^{11}\)

Also, with parenchymal lung destruction the pulmonary vascular bed area decreases in size leading to increased PVR contributing to PH. \(^{32}\)

PH was identified as a predictor of poor outcome in pulmonary disease and was associated with worse exercise tolerance, dyspnea on exertion and decreased survival. \(^{24,32-34}\)

It is important to realize that PH can coincidentally coexist with lung disease without being caused by the latter. \(^{27}\)

This can be suspected when the degree of severity of PH is out of proportion to the coexisting lung disease, in these cases the PH could actually be group A PH and IPAH specific treatment could be sought. Guidelines recommend referral of such patients to a PH and CLD specialized center for further evaluation and management. \(^{27}\)

Currently CLD associated PH is divided into mild-moderate with mPAP 25 mmHg or greater but less than 35 mmHg and severe CLD-PHTN with mPAP 35 or greater or mPAP 25 or greater with cardiac index less than 2.01/minute/m\(^2\). \(^{27}\)

Identifying this latter group is important as it could be a target for clinical trials addressing whether PAH specific treatments could be beneficial to that population.

Chronic Thromboembolic Pulmonary Hypertension (Group 4)

Chronic thromboembolic disease (CTE) is an important cause for PH. It is the result of non-resolving and organized pulmonary artery thrombi leading to increased pulmonary vascular resistance. Multiple factors are believed to hamper resolution of pulmonary thrombi including chronic inflammation, altered angiogenesis, thrombophilia, abnormal fibrin and impaired fibrinolysis. \(^{35}\)

CTE is sometimes overlooked when working up PH, another source of missing the diagnosis is relying on CT pulmonary angiography to rule it out which is not sensitive enough. \(^{36}\)

Ventilation perfusion scan (V/Q) scan is the recommended test to screen for CTEPH. \(^{37}\)

Pulmonary endarterectomy (PEA) and lifelong anticoagulation remain as the standard of care for CTEPH. PEA is a major surgery commonly utilizing the deep hypothermic circulatory arrest technique with the use of cardiopulmonary
bypass machine, thereby evaluation for surgical candidacy should be done in expert centers.\textsuperscript{37} Riociguat is a Food and Drug Administration (FDA)-approved agent for treatment of non-operable CTEPH patients; this will be further discussed in the treatment section.\textsuperscript{37}

**Pulmonary Hypertension with Unclear Multifactorial Mechanisms (Group 5):**

As the name suggests group 5 PH include medical conditions that lead to pulmonary hypertension by multiple pathophysiologic mechanisms, some of which are unclear. Some of these diseases include chronic hemolytic anemia (e.g., thalassemia and sickle cell disease), myeloproliferative disease, post splenectomy states, sarcoidosis and metabolic diseases (e.g., glycogen storage disease and thyroid disorders).\textsuperscript{38} These conditions lead to PH through one or more etiologic factors including precapillary PH, IPAH similar mechanisms, left heart dysfunction and resultant PH, lung destruction and resultant PH and chronic thromboembolic disease.\textsuperscript{38} It is important to be aware of this group of diseases to screen for PH when suspected and initiate the proper evaluation as the presence of PH is a marker of poor prognosis in some of these conditions.\textsuperscript{39-41}

**Diagnosis**

Diagnosis of pulmonary hypertension can be challenging given lack of a specific clinical picture. Evaluation for PH is usually done in the setting of dyspnea evaluation, and the workup done helps identify the cause of PH as well as establishing the diagnosis itself. Workup includes a variety of tests from simple EKGs to invasive right-sided heart catheterization and hemodynamic studies. Being able to identify the cause of PH is important due to the presence of IPAH directed medications that improve hemodynamics and clinical outcomes when used to treat group 1 PH but can be deleterious in some of the other groups of PH.

**Chest X-ray:** It can show enlarged pulmonary artery trunk with decreased peripheral pulmonary vessels. It also can show evidence of lung disease including diffuse lung parenchymal disease or signs of hyperinflation and emphysema suggestive of obstructive lung disease. While CXR may show some clues, the presence of a normal study does not rule out PH.

**Electrocardiogram (EKG):** It can show evidence of right ventricular hypertrophy, right atrial enlargement and right ventricular strain pattern which could indicate elevated pulmonary circulation pressure. Such findings are non-specific.

**Echocardiography:** It remains a very informative tool and the best noninvasive screening tool for PH. It provides estimation of systolic pulmonary artery pressure (a non-invasive estimate of the pulmonary circulation pressure) using measurement of tricuspid regurgitation jet velocity and Bernoulli’s equation. It also provides information on the right atrial and ventricular dimensions, interventricular septum flattening or bowing into the left ventricle which all can be additional clues on the presence of PH.\textsuperscript{41} It provides additional information on the right ventricular (RV) function, remodeling and development of RV failure which is a predictor of poor prognosis in PH.\textsuperscript{42} Evaluation of the left heart systolic and diastolic function in addition to the presence of valvular heart disease helps differentiate between group 1 and group 2 PH. Echo can also help identify the presence of congenital heart disease which could be the cause of PH. It is important to remember that echocardiography provides noninvasive data, while direct measurements of mPAP, PVR, and PAWP by right heart catheterization are required to confirm the diagnosis of PH and in ruling out group 2 PH.

**High resolution computerized tomography (HRCT):** While this is usually aimed at diagnosing parenchymal lung disease in the setting of evaluation for dyspnea, it can also provide clues to the diagnosis of PH. Enlarged PA trunk and PA to thoracic aorta diameter ratio greater than 1 is suggestive of PAH.\textsuperscript{41} Presence of significant parenchymal lung disease in a patient with PH would denote that it is likely WHO group 3 PH. PVOD can have abnormalities on HRCT with mediastinal lymphadenopathy, ground glass opacities and septal thickening.\textsuperscript{34, 41}

**Polysomnography:** Sleep study is helpful in screening for and ruling out sleep-disordered breathing as an etiology for pulmonary hypertension.

**Pulmonary function tests (PFTs):** These provide important information regarding the presence of pulmonary obstructive disease or restrictive disease and the degree of the pulmonary impairment resulting from such disorders. Presence of discrepancy between the severity of PFTS impairment due to a pulmonary disorder and the severity of PH should always raise suspicion for the presence of an IPAH component. It is important to note that IPAH can be associated with mild to moderate reduction in lung volume and decreased diffusion lung capacity of carbon
monoxide (DLCO) which can correlate with the severity of PH. 48

CT pulmonary angiography, CT perfusion and Ventilation/Perfusion studies of the lung: These play a role in identifying CTEPH. Vascular occlusion, pulmonary artery webs, mosaic pattern on perfusion studies is suggestive. These changes can be very subtle findings and require training and experience to diagnosis. 67 High resolution multi detector CT pulmonary angiography (CTPA) may be used as an alternative to conventional angiography for evaluation of CTEPH patients in expert centers while the test of choice for screening remains to be ventilation perfusion (V/Q) scans. 37

Other evaluation modalities of cause of PH: Evaluating for connective tissue disease, HIV infection, hemolytic anemias, sarcoidosis and careful review of medication exposure and family history are vital in identifying possible causes for PH.

Right heart catheterization (RHC): This is the cornerstone in diagnosing and evaluating pulmonary hypertension as the diagnosis of PH requires elevated mPAP 25 mmHg or greater at rest, and the diagnosis of PAH additionally requires PAWP 15 mmHg or fewer and increased PVR greater than 3 wood units. Current recommendations do not advocate for exercise measurement of mPAP to make the PH diagnosis in patients with normal/borderline mPAP at rest. 1 There is interest in using volume loading of left heart and measurement of exercise hemodynamics using RHC to uncover left heart diastolic dysfunction to avoid misclassifying patients as IPAH instead of group 2 PH, but current guidelines advise that there is still need for further standardization and study of such technique before their routine use in clinical practice can be endorsed. 1 RHC is also needed to test for vasoreactivity in patients with PAH. Presence of vasoreactivity is a prerequisite for treatment with high dose calcium channel blockers. This is done by using vasodilators preferably inhaled nitric oxide (NO), a positive response is achieved when mPAP decreases at least 10 mmHg and to a value of 40 mmHg or less. 48, 49

Treatment

General Supportive Measures
Treatment of pulmonary hypertension depends on the type of PH based on the WHO classification with lack of group specific medications except for group 1 – pulmonary artery hypertension. There are general supportive measures that most PH patients would benefit from. These include supervised exercise program, diuretics, digoxin in some cases, anticoagulation and oxygen therapy. 48 Supervised exercise program and rehabilitation was found to increase the quality of life and exercise capacity of patients, this was reflected by improvement of performance on six-minute walk test (6MWT). 60-62 Diuretics can be helpful in the settings of right sided heart failure which can lead to lower extremity edema, ascites, hepatic and bowel congestion, they can also be of use in group 2 patients from the heart failure standpoint. Digoxin may be considered per the most recent WSPH, it is used due to associated acute increase in cardiac output and is preferred in patients with associated tachyarrhythmias. 48, 53 Anticoagulation is considered in IPAH, heritable PAH, PAH due to anorexigens and is indicated in group 3 PH patients (CTEPH), also it may be considered in associated PAH e.g., PAH associated with connective tissue disease. 48 Oxygen therapy is suggested to maintain arterial partial pressure of oxygen of 60 mmHg or more. 48

Treatment of Group 2, 3, 4 and 5 Patients
In general treatment of the underlying condition is the mainstay of treatment. This could include medical treatment for heart failure, lung disease, sarcoidosis and other conditions or it can be a surgical procedure in the case of group 4 patients where PEA is indicated. 27 Current evidence does not support use of PAH directed therapy in LHD-PH, it is important to note though that patients with combined pre and post capillary pulmonary hypertension are a population of interest when it comes to possible benefit to such treatments. 16 In group 3 patients with mild to moderate PH (mPAP 25 mmHg or greater but less than 35 mmHg) no data currently supports use of PAH directed therapy while in those patients with severe PAH (mPAP 35 or greater or mPAP 25 or greater with cardiac index less than 2.01/minute/ m²) use of PAH directed therapy in the setting of clinical trials or on a compassionate basis may be considered, and such patients should be evaluated in expert centers. 27 In contrast to the previous patient groups, CTEPH patients who are not candidates for PEA or have residual PH after PEA are candidates for one of the PAH directed therapy agents; Riociguat which is a soluble guanylate cyclase stimulator. 57 Currently there is no recommendations for use of PAH therapies in group 5 patients. 16 It is important to note that group 2-5 pulmonary hypertension patients would always benefit from evaluation at expert centers and individualization of therapy. There remains a gap of evidence
regarding role of PAH directed therapy in these different groups of patients, but progressive understanding of pathophysiology, standardization of definitions of these patient populations and setting goals for treatments and guidance for future clinical trials would catalyze the production of data to fill this gap.

**Calcium Channel Blockers (CCBs)**

High dose CCBs (amlodipine, nifedipine and diltiazem) are one of the earliest medications to be used in PAH due to the vasodilator effect. They were found to improve prognosis in vasoreactivity testing responders. Vasoreactivity testing is a prerequisite for treatment with CCBs. This is done by using vasodilators preferably inhaled nitric oxide (NO), a positive response is achieved when mPAP decreases at least 10 mmHg and to a value of 40 mmHg or less without decrease in cardiac output. Patients with WHO functional class I – III and positive vasoreactivity response should be treated with CCBs. Monitoring for response to treatment should be done and patients with deterioration or lack of improvement on CCBs or those who failed to show vasoactive response initially should be evaluated for starting PAH directed therapy.

**PAH Directed Therapy**

**Prostacyclin pathway related medications:** This class of medications includes prostanoids which work as prostacyclin/prostaglandin I2 (vasodilator prostaglandin) analogues and the prostacyclin IP receptor agonist; Selexipag. They work by inducing vasodilatation, exhibiting anti-platelet aggregation and anti-proliferative effects. They provide improvement in functional capacity, 6MWT, hemodynamics and uniquely mortality in the case of Epoprostenol. Epoprostenol is the first medication to be approved for PAH treatment, it is administered as a continuous IV infusion through a central catheter, has short half-life and is unstable at room temperatures. More prostanoids were developed in a trial to overcome these shortcomings. Prostanoids are reserved for advanced PAH (drug of choice in WHO functional class IV patients and an option for patients with WHO functional class III) or patients who failed another PAH treatment. Different members of this class of medications are listed in Table 2.

**Endothelin receptor antagonists (ERA):** Over expression of the vasoconstrictor mediator endothelin plays an important role in the pathogenesis of PAH. This class of medications acts by blocking Endothelin receptor A and B to leading to vasodilatation and resultant improved PVR. Both receptors mediate the vasoconstrictor action of endothelin in the pulmonary vasculature, receptor B is also expressed in the endothelial cells but its activation facilitates production of vasodilator prostacyclin and NO. ERA are indicated for PAH patients with WHO functional class II and III and considered for class IV. Different ERA are listed in Table 3.

**Nitric oxide (NO) pathway related medications:** NO is a potent vasodilator of the pulmonary circulation. Under production of NO due to endothelial dysfunction plays an important role in the pathogenesis of PAH. Medications that work on this pathway include phosphodiesterase 5 (PDE5) inhibitors and soluble guanylate cyclase activator (GCa). PDE5 inhibitors act by inhibiting the breakdown

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### Table 2. Members of the prostacyclin pathway

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>IV</td>
<td>Improves mortality; AE include flushing, jaw pain, and catheter related infections.</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>SC, IV, inhaled, and PO</td>
<td>Stable at room temperature. Evidence supporting oral form is contradicting.</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>IV and inhaled</td>
<td>Inhaled form is approved by FDA. It is administered 6-9 times a day.</td>
</tr>
<tr>
<td>Beraprost</td>
<td>PO</td>
<td>Provides short term improvement of exercise capacity. Approved in Japan and South Korea.</td>
</tr>
<tr>
<td>Selexipag</td>
<td>PO</td>
<td>It is not an analogue of prostacyclin but rather prostacyclin IP receptor agonist.</td>
</tr>
</tbody>
</table>

**Table 2 Notes:** IV: intravenous; SC: subcutaneous; PO: per oral; AE: adverse events

### Table 3. Endothelin receptor antagonists

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>PO</td>
<td>Blocks both Endothelin receptors. Improves 6MWT and time to clinical worsening; AE include reversible elevation of liver enzymes; Monitoring of LFTs is required.</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>PO</td>
<td>Selective antagonist blocking endothelin receptor A. Improves functional class, 6MWT, time to clinical worsening and hemodynamics.</td>
</tr>
<tr>
<td>Macitentan</td>
<td>PO</td>
<td>Blocks both Endothelin receptors. Slows down disease progression, decreases hospitalization for PAH and risk of mortality.</td>
</tr>
</tbody>
</table>

**Table 3 Notes:** PO: per oral; AE: adverse events; LFTs: Liver function tests.
of cyclic guanosine monophosphate (cGMP) which is the second messenger through which NO exerts its vasodilator effect. GCa is a new class of medications with Riociguat being an orphan drug in this class, it induces vasodilation through increasing cGMP level by 2 mechanisms. It sensitizes guanylate cyclase to NO to mount an adequate vasodilator response despite low levels of NO, it can also stimulate guanylate cyclase in the absence of NO which is the second mode of action. PDE5 inhibitors and Riociguat are indicated for PAH patients with WHO functional class II and III and considered for class IV.48 Different members of this class of medications are listed in Table 4.

Table 4. Members of the NO pathway PAH medications.

| Sildenafil | PO, IV | Improves 6MWT, functional class and hemodynamics.70,71 The IV formulation can be used as an alternative when medications cannot be administered orally for patient related factors. |
| Tadalafil | PO | Improves 6MWT, functional class, time to clinical worsening and hemodynamics.72 |
| Vardenafil | PO | Improves exercise capacity, time to clinical worsening and hemodynamics.73 Is not FDA approved for PAH treatment. |
| Riociguat | PO | Improves 6MWT, time to clinical worsening and hemodynamics.74 It is also indicated in non-operative CTEPH.75 |

PO: per oral; IV: intravenous.

Combination Therapy

Combination therapy can be done in one of two fashions, either upfront combination therapy or sequential combination therapy in cases of lack of response to initial monotherapy. The 2014 chest guidelines suggest the sequential approach while the 2015 European Society of Cardiology guidelines equally recommended either approaches.75,75 Different combinations include ERA plus a PDE5 inhibitor/Riociguat or a prostanoid plus an ERA or a prostanoid plus a PDE5 inhibitor/Riociguat, triple therapy is attempted if double therapy did not result in clinical response.80

Non-medical Management

This includes pulmonary endarterectomy (PEA) for CTEPH, pulmonary artery angioplasty, balloon atrial septostomy and lung transplantation. As discussed earlier PEA is the treatment of choice for CTEPH. Use of percutaneous pulmonary artery angioplasty was reported in case reports with adequate hemodynamic results but further evaluation of patient selection criteria, durability and studying follow up data is needed.76-79 Balloon atrial septostomy is currently considered as a bridge to lung transplantation or a palliative measure.80 Lung transplantation is considered in the presence of inadequate response to medical therapy.80

Conclusion

Pulmonary hypertension is classified into five groups by the WHO. For group 2, 4 and 5 the mainstay of management is treating the underlying cause. For group 3, PEA is the main treatment with Riociguat being an option in selected patients. Medical treatment options of group 1 continue to expand, hence it is very important when faced with patients with pulmonary hypertension to properly classify those patients into the right WHO group. It is also important to make appropriate early referral to a specialist who can further manage this patient population.

REFERENCES


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safe sleep ABCs

**A** lone **B**ack **C**rib

Babies should sleep **alone**, on their **backs**, and in a **safe crib**.

As providers, we know safe sleep practices save lives. Remind your patients that *room sharing is recommended but bed sharing is not*. Babies should never share any sleep surface with an adult, a child, or a pet.

To find out more about the American Academy of Pediatrics’ Recommendations for a Safe Infant Sleeping Environment, go to [ForBabySakeSD.com/training](http://ForBabySakeSD.com/training).

Encourage your patients to follow these simple ABCs at every sleep time.

_for baby’s sake_
Overview and Management of Small Bowel Obstruction versus Ileus: A Primer for All Physicians

By Jesse Van Maanen, MD; Hassan Turaihi, MD; Paula Denevan, MD; and Thavam Thambi-Pillai, MD, MBA, FICS, FACS

Abstract
The conditions of small bowel obstruction and ileus are ones with a great deal of overlap with respect to presentation and differential diagnosis but vary substantially with respect to management. These disorders are frequently encountered by members of the healthcare team across almost every specialty in one way or another. Understanding safe and expeditious methods to identify and distinguish these conditions is important for all providers to understand. This article aims to compare both disorders, briefly discuss the pathophysiology and presentation, give a differential diagnosis for these disorders, and pursue a course of diagnosis and therapy in an appropriate, safe, and cost-effective manner.

Small Bowel Obstruction
Introduction
Small bowel obstruction (SBO) refers to a process in which the flow of enteric contents through the small intestine cannot pass in a normal manner. This can be due to an intraluminal, extraluminal, mechanical, or functional problem. Most cases are due to extraluminal and mechanical forces, which will be the focus of this review.

Although mechanical bowel obstruction can be safely and preferably managed nonoperatively much of the time, they can be a surgical emergency. The decision to operate is directed by the etiology and severity of the obstruction. The greatest concern when a patient is suffering from a SBO is the potential sequelae on the spectrum from bowel dilation, to ischemia, necrosis, and possible perforation.¹

Some of the major risk factors for the development of SBO include previous abdominal or pelvic surgery, hernias, intra-abdominal inflammation, history of cancer, or radiation to the abdomen/pelvis. Additionally, the likelihood of SBO recurrence is directly correlated to the number of previous small bowel obstructions. By far the most frequent cause for SBO in the U.S. is adhesions, followed in descending commonality by tumors, hernias, IBD, and others among which volvulus and intussusception are possibilities (Figure 1).²³ The cause for adhesion formation in patients with no previous regional surgery is intra-abdominal inflammation caused by entities such as diverticulitis or Crohn’s disease which form adhesions during healing.¹ Women may form adhesions secondary to pelvic inflammatory disease or other gynecologic infections.

Pathophysiology
Although obstruction may originate outside, within the wall, or within the intestinal lumen, its effect is the same. Early in the course of an obstruction, intestinal motility and contractile activity increase in an effort to overcome the area of blockage. The increase in peristalsis that occurs

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Figure 1. Causes of small bowel obstruction in the U.S.
early in the course of bowel obstruction is thought to be the cause of the colicky abdominal pain and accounts for the finding of diarrhea that may accompany partial or even complete small bowel obstruction in the early period. Later in the course of obstruction, dilatation of the proximal bowel segment occurs as backup of enteric contents and air are prevented from passing beyond the obstruction. With time the intestine becomes dilated and contractions becoming less frequent and less intense.

As the bowel dilates, transudative fluid shifts and bowel wall edema occur. This massive third-space fluid loss accounts for the dehydration and hypovolemia. As the bowel becomes progressively edematous and dilated, the absorptive function declines, and acid-base derangements can result. With increasing intraluminal pressure the small intramural blood vessels supplying the mucosa are unable to adequately perfuse the most luminal regions of the intestine. This can lead to tissue ischemia, necrosis, and eventual perforation if perfusion is not restored. It is important to remember that luminal and vascular obstruction can also be due to twisting or kinking by processes such as a volvulus, internal hernia, adhesive bands, or other mass effect.

Presentation
The clinical presentation of SBO varies depending on the chronicity, severity, and location of the obstruction but most commonly entail nausea and vomiting (77-82 percent), crampy abdominal pain (68-92 percent), abdominal distention, and obstipation (52-90 percent). These are especially true when the SBO is severe and acute. Obstruction points distal in the small bowel have more distention than those located more proximally. Chronic or partial SBO may present with similar symptoms but are often more indolent and less severe. When nausea and vomiting is present patients are often unable to keep up with oral intake. Inquiring about the aforementioned signs/symptoms is important when taking a patient history. Fever may also be present. Physical exam may demonstrate signs of dehydration. The abdominal exam finds distention in 56-65 percent of patients. Palpation of the abdomen will likely exacerbate pain and often high-pitched “tinkling” sounds are heard in the acute SBO. Evaluation for abdominal and groin hernias should not be overlooked as these can be the cause.

There are a few circumstances whereby presentation may differ. Closed-loop obstruction from a hernia or volvulus may present with less distention, especially if the loop is small, as there is both no patent inlet or outlet to the problem segment. This type of obstruction may also present without a significant lactic acidosis if venous outflow is impeded. Closed-loop obstructions have a higher rate of perforation due to these same principles – decompression is hindered. Chronic or partial SBO often presents with postprandial abdominal pain and varying degrees of nausea and vomiting.

D iagnosis
After a thorough and pertinent history and physical examination, laboratory and imaging modalities are often used to aid in the diagnosis. Typically, a complete blood count with differential and electrolyte panel are obtained. If patients are exhibiting systemic signs (tachycardia, hypo- or hypertension, fever), arterial blood gas and serum lactate are often obtained. Serum lactate is a sensitive (90-100 percent), though not specific (42-87 percent) test for ischemia related to a SBO. Vomiting can lead to dehydration and the classic finding of hypokalemic, hypochloremic metabolic alkalosis. Ischemia and necrosis of the bowel can also produce a metabolic acidosis.

Imaging is almost always required to confirm the diagnosis, as the differential is broad and includes, but is not limited to: paralytic ileus, pseudo-obstruction, and large bowel obstruction. Plain radiographs and computed tomography (CT) scan are the most commonly used imaging modalities. Other imaging modalities such as abdominal ultrasonography and magnetic resonance enterography can be used in the diagnosis of SBO but are less diagnostic and will not be discussed in this review.

Plain radiography is useful for identification of patients who may need immediate surgical intervention. Findings that suggest against conservative treatment include free intraabdominal air or intestinal pathology such as sigmoid or cecal volvulus. Typical findings of SBO in an upright (or lateral decubitus) and supine series includes: dilated small bowel loops (defined as greater than 3 cm in diameter), air-fluid levels, and proximal bowel dilatation with distal decompression (Figure 2). Unfortunately, plain films can be equivocal in 20-30 percent and misleading in 10-20 percent of cases. In a stable patient who does not meet criteria for immediate surgical intervention based on physical exam and plain abdominal X-ray, a CT scan is a helpful next test.

A CT scan of the abdomen and pelvis should be
performed with intravenous contrast in patients without contraindications. Oral contrast is sometimes used, but patients can often not tolerate oral intake in this setting. This more specific test can delineate the transition point (area of obstruction) and severity, in addition to bowel wall thickening, intra-abdominal ascites, mesenteric edema, hemorrhage, pneumatosis intestinalis, portal venous gas, and more (Figure 3). Complications such as edema, necrosis, and perforation are more readily seen on CT than compared with plain radiograph.9,10

Management

With the diagnosis of SBO made, the most important decision is whether the patient warrants immediate operative intervention. This usually necessitates a surgical consult. An acute abdomen/peritonitis on physical exam, findings of intestinal ischemia, necrosis, or perforation, closed-loop obstruction, or sepsis are common indications for exploration. Other signs and symptoms may warrant surgical exploration including tachycardia, fever, leukocytosis, and constant abdominal pain. However, no specific laboratory or imaging studies can accurately detect or exclude the presence of threatened bowel and high index of suspicion is the key for an accurate and timely diagnosis.

In most cases, patients present with an acute but not immediately life-threatening SBO. If the obstruction is partial and symptoms are mild and due to chronic diseases such as enteritis, outpatient management can be utilized. In this setting, the cause is addressed and patients are instructed to consume a liquid diet to keep up with caloric needs for a short period with close follow-up. More often, however, patients require admission for monitoring.

Initial non-operative management includes admission to the hospital, nil per os (NPO) status, proximal bowel decompression with a nasogastric tube, IV fluid resuscitation and maintenance with crystalloid solution, electrolyte replacement, serial abdominal exams, and pain and nausea control. Optimization of other chronic medical problems should not be ignored and medications via IV route are encouraged while the patient is NPO. Antibiotics are not encouraged in uncomplicated SBO. Contrast studies can be utilized as well. This entails the administration of hyperosmolar enteral contrast followed by an abdominal plain film taken four to eight hours later. Passage of contrast into the colon suggest at least the beginning resolution of the obstruction, and conservative management is continued. Contrast that does not pass into the colon on repeated imaging indicates a high-grade bowel obstruction that is unlikely to resolve without surgical intervention. This test can serve both diagnostic and therapeutic functions, as the hyperosmotic contrast can pull fluid from the bowel wall, reducing edema, and potentially relieving the obstruction. Conservative management of adhesive SBO is effective in up to 80 percent of cases.11
with return of bowel function within an average of two to five days. After bowel function returns, diet is usually slowly advanced over the course of a few days to weeks back to regular foods.

Many studies have attempted to predict the efficacy of conservative management and the subsequent need for operative intervention based on initial presentation. A study published in 2010 aimed to identify clinical signs which might indicate the ultimate need for operative treatment. They discovered four independent clinical signs that held positive predictive value (PPV) for the need for an operation: vomiting, lack of small bowel feces sign, mesenteric edema, and free intraperitoneal fluid. The small bowel feces sign is a finding on CT scan whereby particulate fecal material is seen within the small intestine. This is more likely found in the colon where water absorption occurs. The presence of this sign suggests that stool found there is chronic, leading to water absorption by an area of the GI tract not principally responsible for this action. PPV regarding the need for an operation were 90 percent, 70 percent, 55 percent, and 0 percent for all four, three, two, and one or zero of these findings, respectively. An algorithm for the decision to proceed to the operating room was also developed and can be found in their publication.

When surgery is required, both laparoscopic and open techniques have been used with success. In the past, laparotomy was the method of choice but with advancements in laparoscopic technique, rates of overall complications have fallen dramatically with this method (surgical site infections, intraoperative transfusions, hospital length of stay, and overall mortality). When laparoscopy is not safe or effective, such as in patient with many previous abdominal surgeries, dense adhesions, distal obstructions, or when laparoscopy is attempted but unable to relieve the obstruction, laparotomy is used. After surgery, guidelines for returning to diet and activity are similar to those for other comparable bowel surgeries. A diet high in fiber is important once the obstruction is completely resolved. There is generally no reason to keep a patient on a soft/liquid, or low fiber diet permanently, but is often utilized for the first weeks after resolution and discharge.

Ileus

Introduction

An ileus (origin: Greek 'eileos'-twisting), or aperistalsis and loss of coordination of gastrointestinal (GI) motility, can in many ways mimic a mechanical small bowel obstruction. Frequently ileus is the result of a noxious or injurious insult. Distinguishing ileus from mechanical small bowel obstruction is important since management strategies have some differences. A postoperative ileus (POI) is a common problem for surgical patients. Nearly all experience this condition to some degree following abdominal surgery, and POI is considered the most common reason for delayed hospital discharge. Not all episodes of ileus are due to abdominal surgery. Peritonitis and abdominal infection, trauma, electrolyte abnormalities, intestinal ischemia, and medications are common causes of ileus formation. The evaluation and management of ileus due to non-surgical causes is roughly the same with small differences which will be highlighted.

It is important to understand the difference between an expected (physiologic) POI and a prolonged ileus. Following all abdominal surgery, the GI tract responds with some degree of ileus. Physiologic POI length varies depending on the segment of the GI tract involved. Generally speaking, the small intestine has the shortest recovery period at 0-24 hours. The stomach usually recovers between 24-48 hours. The colon has the slowest return to normal motility following abdominal surgery when no other complicating factors are present at around 48-72 hours. Prolonged POI is thus pathologic and exists when there is absence of return of bowel function (flatus or stool passage) beyond the expected time frame, defined as beyond five days after surgery. The duration of an ileus also depends on the type of surgery performed.

Risk factors for POI include: prolonged abdominal or pelvic surgery, aggressive handling of the bowel during surgery, lower GI tract surgery, open surgery, a delay in enteral nutrition, routine nasogastric tube placement, intraabdominal inflammation/infection, perioperative bleeding, and opioid use.

Pathophysiology

The topic of GI function and motility is complex, and one to which an entire other article could be devoted. In brief, both intrinsic and extrinsic neural networks exist which contribute to GI motility. The intrinsic system is located within the gut wall, known as the enteric nervous system. This system will respond to extrinsic signals but also has the reflexive ability to respond independently to stimuli. Extrinsic signaling comes from the autonomic nervous system, primarily from the vagus, splanchnic, and pelvic...
nerves. Both the intrinsic and extrinsic pathways have inhibitory and excitatory stimuli.

Broadly speaking, there are three influencing mechanisms through which a POI can form: inflammation, inhibitory neural reflexes, and neurohumoral peptides. Surgery, in general, produces heightened levels of proinflammatory cytokines from macrophages such as interleukin-6, cyclooxygenase-2, and inducible nitric oxide (NO) synthetase. Degranulation of mast cells also contributes to the inflammatory pathogenesis of ileus. Focal manipulation of bowel causes localized increase in these inhibitory cytokines, but studies suggest a pan-enteric release also exists. In addition to inflammation secondary to routine surgery, regional and systemic inflammation from entities such as intraabdominal abscesses, anastomotic leaks, appendicitis, cholecystitis, hemoperitoneum, pancreatitis, sepsis, and uremia, just to name a few, can also cause an ileus.

Secondly, neural reflexes are also known to contribute to ileus through noxious spinal afferent pathways which increase inhibitory sympathetic activity to the gut. The increase in this activity has been observed secondary to extensive abdominal surgery. Neurohumoral peptides are the third broad mechanism responsible for physiologic POI. The most prominent peptides include endogenous opioids, calcitonin gene-related peptide, motilin, substance P, and vasoactive intestinal peptide. These act as inhibitory neurotransmitters to intrinsic gut motility. The topic of exogenous opioids is currently being discussed widely due to the overuse and dependence epidemic, but also has implications in GI motility. It is well known that opioids result in delayed gastric emptying and non-propulsive smooth muscle contraction in the GI tract through binding to mu and kappa receptors. Other drugs with anticholinergic and antihistamine mechanisms of action contribute to ileus formation and prolongation.

Presentation
The presenting symptoms of an ileus are often indistinguishable from a bowel obstruction. Abdominal distention, bloating, abdominal pain, nausea, vomiting, intolerance to by mouth intake, and decreased passage of flatus or stool are common. Although easily confused with a SBO at first, some important distinctions exist. Pain related to an ileus is often more diffuse and non-specific. Fever does not usually accompany an ileus, but should raise suspicion for a SBO if that is a concern.

Physical exam will often demonstrate abdominal distention and tympany. Diffuse tenderness is often evident, without signs of peritonitis. Quiet or absent bowel sounds suggest an ileus, in contrast to high-pitched sounds more often seen during a SBO.

Diagnosis
No diagnostic test can confirm or exclude the diagnosis of postoperative ileus with certainty. Generally the diagnosis of an ileus is made through the presence of signs and symptoms, physical exam findings, laboratory values, and imaging. In most cases, limited imaging is required.

Laboratory values are non-specific but may help reveal the cause of the ileus. A complete blood count may reveal anemia suggestive of postoperative hemorrhage, or leukocytosis suggestive of inflammation, infection, or ischemia. Electrolyte derangements similar to that found during a SBO are common if vomiting has occurred. Additionally, hypokalemia is known to worsen an ileus. Magnesium should be checked as hypomagnesemia can lead to hypokalemia refractory to replacement attempts.

When a SBO is suspected, the first image obtained is often an abdominal X-ray which will show diffuse gaseous distention of small bowel and often gas within the colon. If a CT scan is obtained, SBO vs ileus is more easily delineated, as there is no transition point seen with an ileus. Sometimes it is difficult to define an ileus from a partial SBO. In this case, an upper GI contrast study with water-soluble contrast is sometimes obtained.

Management
Fortunately, most episodes of POI are self-limiting. There is no role for surgical or endoscopic intervention in the management of a routine postoperative ileus as reviewed here. It is worth mentioning that management of colonic pseudo-obstruction (Ogilvie syndrome), a unique type of adynamic colonic ileus, is not discussed within this review but can progress to require operative or procedural treatment. While a POI must ultimately resolve with time, there are a number of interventions that have shown to be effective in reducing its duration.

Prevention of neural inhibitory reflexes with the use of spinal epidural anesthesia has been shown to be effective for the first 48-72 hours postoperatively. This also has the opportunity to lessen the use of opioids and their negative effects.
effects on GI motility.

Neurohumoral peptide antagonism is also effective. VIP, NO, and substance P inhibitors block these peptides whose function is to reduce GI motility. In addition to antagonizing inhibitor molecules, augmenting and stimulating promotility hormones has been effective. Erythromycin acts as a motilin agonist, thereby promoting GI motility. Metoclopramide’s effects are two-fold: nausea control plus gastroprokinetic activity by way of antagonism of D2 receptors and agonistic effects on 5-HT4 and muscarinic receptors. Avoiding opioid overuse is also important. Diversified non-narcotic medication used as first line treatment of pain is not only the responsibility of every physician who prescribes pain medication, but it can also help reduce ileus in the perioperative period. When judicial use is indicated, alvimopan and methylnaltrexone are drugs with peripheral mu receptor antagonism which do not cross the blood-brain barrier, thereby reducing ileus-inducing side effects without decreasing pain control efficacy.17,19,20

Normovolemia and as-needed electrolyte replacement (specifically magnesium and potassium) are important as well. These can be easily forgotten if not paid attention to. Interestingly, gum chewing has been shown to reduce the duration of ileus in some studies. The postulated mechanism of action is stimulation of the vagal cholinergic pathway leading to increased release of pro-motility mediators. Early feeding has been shown to stimulate pro-motility factors as well, but if done too aggressively may lead to nausea/vomiting and be poorly tolerated.

While many quote mobility/walking as a treatment for ileus, this has not been shown to be independently effective. Nonetheless, ambulation is important for many other reasons and should not be discouraged.21 There is limited data on the efficacy of laxatives in ileus and are generally not used. Nasogastric decompression can and should be used if the patient is significantly nauseated or vomiting to help alleviate symptoms and reduce aspiration risk, but routine use has been shown to prolong ileus and cause undue discomfort.

Of course, methods for prevention are also important. Minimizing trauma, proper tissue handling techniques, laparoscopic compared with open surgery, and prompt correction of intra-abdominal infections and abscesses, anemia, and intestinal ischemia can reduce the severity or even prevent a clinically significant ileus.17,19

Summary

Small bowel obstruction and ileus are common problems among medical and surgical patients and often present with overlapping features. As outlined in this article, differences exist between presentation, pathophysiology, workup, and management. We hope that this has served as a helpful review of these conditions and made recognition and initial management more easily understood, translating into better care for all of our patients.

Acknowledgement: The resident authors would like to thank the many patients we serve who teach us every day.

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Traditionally the treatment of deep-seated infections such as osteomyelitis, joint infections, and endocarditis has necessitated 6 week or longer courses of intravenous (IV) antibiotics. These infections often involve prosthetic devices and can be difficult to resolve, which has contributed to the long courses of IV therapy. Current guidelines recommend four to six weeks of IV or highly bioavailable oral therapy for treatment of vertebral osteomyelitis, four to six weeks of IV or highly bioavailable oral therapy for prosthetic joint infections, and two to six weeks of IV therapy for treatment of endocarditis, depending upon the pathogen.1-3 The use of IV therapy adds cost, logistical challenges, and time commitment for patients, as well as increasing the risk of complications from IV catheters. Two recently published trials have evaluated the efficacy of the conversion to oral antibiotics for treatment of these types of infections.

The OVIVA trial (Oral versus intravenous antibiotics for bone and joint infection) was a multicenter, noninferiority, randomized, open label trial in the United Kingdom that compared IV versus oral antibiotic treatment in 1,054 patients with bone and joint infections that ordinarily would be treated with a six-week course of IV antibiotics.4 Eligible participants were 18 years or older with an acute or chronic bone or joint infection including vertebral or extra-axial osteomyelitis, native or prosthetic joint infections, or orthopedic fixation device infections. Pertinent exclusion criteria included Staphylococcus aureus bacteremia on presentation or within the previous month, infection by an organism without a suitable oral antibiotic option, concomitant infection that would require a prolonged IV antibiotic course, and mild osteomyelitis requiring less than 6 weeks of antibiotics. Patients randomized to oral antibiotics were switched to oral treatment within seven days of surgery or the start of antibiotic therapy. Infectious disease specialists chose the oral antibiotics based upon culture results and patient specific factors. Adjunctive oral rifampin was allowed in both groups. The primary endpoint was definitive treatment failure within one year after randomization, defined as the presence of at least one clinical, histological, or microbiological indicator of infection. Primary endpoints were identified on follow-up and categorized by three independent specialists blinded to the treatment groups.

Organisms identified (from most to least frequent) were Staphylococcus aureus (methicillin-resistance (MRSA) was identified in only 19 participants), coagulase-negative staphylococcus, streptococcus, pseudomonas, and other gram-negative organisms.4 The most common antibiotic classes used in the IV group were glycopeptides and cephalosporins, and in the oral group were quinolones, combination therapy, and penicillins. Treatment failure in the modified intention-to-treat population occurred in 74 of 506 participants (14.6 percent) in the IV antibiotic group and 67 of 509 participants (13.2 percent) in the oral antibiotic group. The absolute difference in definitive treatment failure between the two groups was -1.4 percentage points (90 percent CI, -4.9 to 2.2). This met the pre-defined non-inferiority margin since the upper limit of the 90 percent CI was less than 5 percent (original study design) and less than 7.5 percent (revised margin after interim analysis). Data from the intention-to-treat and per-protocol populations were similar, and a “worst-case” scenario for missing data also yielded a non-inferior result with the 7.5 percent margin. Median total length of antibiotic treatment was 78 days in the IV group and 71 days in the oral group (p=0.63). Median length of hospital stay was significantly longer in the IV group compared to the oral group (14 days vs. 11 days, p<0.001). Catheter complications were more common in the IV group (9.4 vs. 1 percent), but serious adverse events were not found to be significantly different between the IV group and the oral group (27.7 vs. 26.2 percent, p=0.58).

Strengths of the trial included broad inclusion criteria representing a large patient population, similar baseline...
A similar trial conducted in Denmark compared traditional IV antibiotic treatment of endocarditis to initial IV treatment completed with oral therapy. The POET study (Partial Oral Treatment of Endocarditis) evaluated 400 adults with left sided endocarditis and positive blood cultures for selected common pathogens. All participants were clinically stable and demonstrated a satisfactory response to initial treatment with IV antibiotics. Patients were excluded if they had impaired immune function due to a medication or disease state, evidence of abscess on transesophageal echocardiogram, another indication for prolonged IV therapy, evidence of reduced adherence or potential for reduced oral absorption, or a body mass index greater than 40. After at least 10 days of guideline recommended IV antibiotics, or at least seven days of IV antibiotics after valve surgery, patients were randomized to complete their full course of antibiotics with either in-hospital IV antibiotics, or with oral antibiotics. When possible, the oral antibiotics were administered in an outpatient clinic where patients were closely monitored two to three times weekly. The oral regimens consisted of a combination of two antibiotics from different drug classes, each with moderate to high bioavailability, chosen based upon pathogen susceptibility. Antibiotics used included moxifloxacin, amoxicillin, clindamycin, rifampin, dicloxacillin, fusidic acid, and linezolid. Prior to the completion of their assigned antibiotic treatment, a second transesophageal echocardiogram was completed to ensure adequate clinical response. The most common organisms were streptococcus (45 percent), Enterococcus faecalis (25 percent), Staphylococcus aureus (22 percent), and coagulase-negative staphylococcus (6 percent). No MRSA or other resistant pathogens were identified. After randomization, the group receiving continued IV therapy (n=199) stayed in the hospital to receive antibiotics for a median of 19 days, while the oral treatment group (n=201) was discharged after a median of three days. The oral group received a median of 17 days of post-randomization antibiotics, and 80 percent were partially or completely treated as outpatients.

The primary outcome measured was a composite of all-cause mortality, unplanned cardiac surgery, an embolic event, or a recurrence of bacteremia with the primary pathogen. During six months of follow-up, this endpoint occurred in 24 patients (12.1 percent) in the IV group, compared to 18 (9 percent) in the oral group, which met noninferiority criteria (between-group difference 3.1 percent; 95 percent CI, -3.4 to 9.6; P=0.4). Adverse effects from the antibiotics were similar between the two groups, and occurred in 6 percent of the IV group compared to 5 percent of the oral group (P = 0.66), with the most commonly reported events being allergic reactions, bone marrow suppression, and gastrointestinal side effects.

After an extended 3.5 years of follow-up, oral therapy was not found to be associated with delayed treatment failure. The original composite endpoint occurred in 76 (38.2 percent) of patients in the IV group, compared to 53 patients (26.4 percent) in the oral group (HR 0.64, 95 percent CI 0.45-0.91). Overall, 87 patients died within the extended follow-up timeframe, 54 (27.1 percent) in the IV group, compared to 33 (16.4 percent) in the oral therapy group (HR 0.57, 95 percent CI 0.37 – 0.87). There were no significant differences in unplanned cardiac surgery, embolic events, or infection relapse.

Overall, this study showed that in clinically stable patients who achieved an adequate clinical response after at least 10 days of initial IV treatment, switching to oral antibiotics to complete therapy was not inferior to a full course of IV antibiotics. Clinical application of these results, however, requires a clear understanding of its limitations. The study population was limited to patients with left sided endocarditis due to streptococcus, Enterococcus faecalis, methicillin sensitive Staphylococcus aureus, or coagulase-negative staphylococci; none of the pathogens isolated displayed antimicrobial resistance. The study had very strict inclusion criteria such that only 20 percent of the screened population was randomized to participate. Additionally, 20 percent of the oral group completed their regimen in the hospital, while outpatients receiving oral...
therapy were monitored two to three times per week. Finally, this study was not powered for subgroup analysis, so it is unclear if outcomes were consistent amongst the various pathogens and/or oral treatment regimens.

These trials challenge the traditional use of a six-week course of IV antibiotics for endocarditis and bone and joint infections. The OVIVA trial is stronger, due to its broader inclusion criteria, and based upon its results it would be reasonable for providers to consider transitioning to a targeted oral antibiotic after a short (seven day or less) course of IV antibiotics in the treatment of bone and joint infections. The POET trial, with much more selective inclusion criteria, can be used to support the switch to oral antibiotics in carefully selected, clinically improving patients with left sided endocarditis due to non-drug resistant pathogens who can be carefully monitored during oral therapy. Additional clinical trials are warranted prior to widespread adoption of oral treatment due to the lack of specific antibiotic and microorganism outcomes in both trials. Reducing the duration of IV therapy for appropriately selected patients is likely to reduce the complexity of care, health care costs, and potential complications associated with parenteral therapy.

**REFERENCES**


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Facilities that care for the elderly and disabled face multiple complicated factors affecting their residents and the providers caring for them. Long-term care (LTC) is subject to extensive regulatory and reimbursement elements that continue to evolve, along with required mandated quality reporting. Appropriate hospital admission criteria and reducing avoidable readmissions requires timely, effective communication and coordination of care. Approximately one in five Medicare beneficiaries are discharged from acute hospital care to post-acute care at a skilled nursing facility (SNF). 1

The Patient Driven Payment Model (PDPM), a reimbursement change intended to improve SNF therapy focus, will change later this year and emphasize the condition of the patient rather than the volume of the services provided. Providers, regardless of specialty or location, can assist their LTC colleagues by becoming aware of these changing elements. Emergency department staff, hospitalists, and specialty consultants can help coordinate outpatient care, increase efforts around antibiotic stewardship, reduce adverse medication events, and understand the very fragile condition of many LTC residents. Collaboration is essential to avoid duplication of services and promote patient safety.

All Cause Harm Prevention in Nursing Homes was published in November of 2018. 2 It is a change package to help prevent adverse events, abuse and neglect in nursing home residents. This is a readily accessible resource focused on successful practices in high-performing facilities. It covers a wide range of strategies to promote resident safety and help direct administration and staff leadership. The intended audience includes nursing homes participating in the National Nursing Home Quality Collaborative led by the Centers for Medicare & Medicaid Services (CMS) and the Quality Improvement Organization-Quality Innovation Network (QIO-QIN) organizations across the nation.

The staff at Great Plains Quality Innovation Network (QIN) is dedicated to supporting common goals and offering assistance to LTC staff to promote care in their facilities. They can offer education through Learning Action Networks, newsletters and site visits to help facilities deal with the multiple changes.

Maintaining adequate staffing ratios is always a challenge, especially with the significant turnover in many facilities and the need to train the newly hired. Inadequate funding for patients with Medicaid as their payer source has reached crisis status for a number of nursing homes in South Dakota and will remain an ongoing problem.

Adaptation to organizational change will require leadership from both management and providers. This can assist the patient care staff in promoting teamwork and communication. It is certainly necessary to have resident and family engagement. Open dialogue between family members and caregivers concerning realistic expectations is crucial to help avoid dissatisfaction or complaints. Those involved in LTC, both as patients and providers, will need to adapt to change with continuous education and quality improvement. In LTC, as with all of healthcare, the only thing constant is change.

REFERENCES

1. Health Affairs 38:4 2019
When in life does one come to confront the tough truth that each of us will eventually die? In my years as an internist caring for young and old alike, some people understand this early, and some people never get it. In denying death, we intensify our fear of it. Usually, however, it is sometime during their 50s that people first look into the eyes of death. Put it off as we may, the hard certainty is that we are all aging and one day an end will come. Shakespeare described advanced age in his play As You Like It, Act II, Scene VII (All the world’s a stage):

"... Last scene of all, That ends this strange eventful history, Is second childhood and mere oblivion, Sans (without) teeth, sans eyes, sans taste, sans everything."

Shakespeare’s description of advanced age during the 1600s is rather bleak and scary. I think, with modern medicine and the support of a loving family, we could do better. I clearly believe that advanced age and facing our own death should not fill us with dread. The following is a more hopeful version to end Shakespeare’s excerpt:

"... He did not have to end his life alone; If over time he'd shared his caring, raised the worth of others, fed the love he'd sown. His death would find him kindly prized and praised, While kin sang festive songs of joy, amazed."

Fear of dying can prevent us from making plans about end-of-life care and, most importantly, prevent us from talking to our families about those wishes. How do we want to be cared for if we should lose mental capacity from a stroke or dementia? Do we wish to have a feeding tube, resuscitation, antibiotics when there is no quality of life left, when one doesn’t recognize family and when the only option will be residing in a bed somewhere “sans everything?”

I would rather die and be:

"... kindly prized and praised, While kin sing festive songs of joy, amazed."
Thank you for your membership in the South Dakota State Medical Association. As a member, you have several direct opportunities to become more involved in the important work of the SDSMA:

• Doctor of the Day – serve as the physician for the South Dakota State Legislature for one day during session;
• Physician lobbyist – serve as a volunteer lobbyist during the legislative session;
• SDSMA PAC – help friends of medicine become elected officials and lawmakers;
• SDSMA committees and task forces – serve the organization and yourself;
• SDSMA appointments to state boards, committees and commissions – the SDSMA is asked to nominate and recommend physicians to fill positions to numerous vacancies every year;
• Districts and specialty societies – for local involvement.

If you’d like to get involved, give us a call at 605.336.1965 or visit www.sdsm.org for more information.

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

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**Registration Deadline Approaching – Join us for the 2019 SDSMA Annual Leadership Conference**

The 2019 SDSMA Annual Leadership Conference is in Sioux Falls at the Hilton Garden Inn Downtown on May 31. The 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 below. Annual Leadership Conference is a benefit of your membership. For the latest details about exciting events taking place during the 2019 SDSMA Annual Leadership Conference, sdsm.org. Buy your tickets for the banquet and SDSMA PAC lunch online.

### Friday, May 31

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>8 a.m.</td>
<td>Update from American Medical Association — David O. Barbe, MD, MHA, Past President, AMA</td>
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<tr>
<td>8:45 a.m.</td>
<td>“What is Predictable is Preventable: Fostering Resilience and Recover in the Face of Trauma” – Charity H. Evans, MD, MHCM, FACS, Trauma Surgeon, Nebraska Medicine/University of Nebraska Medical Center; Founder, Dusk to Dawn Youth Violence Prevention Program, Omaha</td>
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<tr>
<td>9:45 a.m.</td>
<td>“A Pandemic of Violence: The Role of Health Care Providers in Preparedness and Response (With an Assist from W. Shakespeare)” – James J. James, MD, PhD, MHA, Executive Director, Society for Disaster Medicine and Public Health; Editor-in-Chief, Disaster Medicine and Public Health Preparedness</td>
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<tr>
<td>10:45 a.m.</td>
<td>Panel Discussion: The Impact Violence has on the Health Care Community – Brad Archer, MD; Mike Elliott, MD; Charity Evans, MD; Blake Gustafson, MD; Jim James, MD; Matt Owens, MD; Matthew Sorrell, MD</td>
</tr>
<tr>
<td>11:45 a.m.</td>
<td>Update from the University of South Dakota Sanford School of Medicine — Tim Ridgway, MD, Executive Dean/Dean of Faculty Affairs, USD SSOM</td>
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<tr>
<td>12:15 p.m.</td>
<td>SDSMA PAC Lunch: Greg DeSautel, MD, Secretary, South Dakota Department of Social Services</td>
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<tr>
<td>1:30 p.m.</td>
<td>Membership Open Forum To submit a policy issue, visit sdsm.org.</td>
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<tr>
<td>2:30 p.m.</td>
<td>Policy Council Meeting</td>
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<tr>
<td>6 p.m.</td>
<td>Membership Mixer</td>
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<tr>
<td>7 p.m.</td>
<td>Awards Banquet, Scholarship Recognition &amp; Presidential Inauguration</td>
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<tr>
<td>9 p.m.</td>
<td>Dessert Reception</td>
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Those who need a hotel room may call the Hilton Garden Inn at 605.444.4704 and ask for the South Dakota State Medical Association block or find a link to the Hilton’s SDSMA reservation homepage at sdsm.org.
Mixer and Banquet is May 31

Members are invited to the SDSMA’s Membership Mixer from 6-7 pm Friday, May 31 at the Hilton Garden Inn, Downtown Sioux Falls during the 2019 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 and Presidential Inauguration following the mixer. To buy banquet tickets, please visit sdmsa.org or call 605.336.1965. Please purchase your tickets by May 20.

Join Us for Awards Banquet & Scholarship Recognition

Enjoy a fun-filled evening of celebration Friday, May 31 at the 2019 SDSMA Annual Leadership Conference at the Hilton Garden Inn, Downtown Sioux Falls.

Start the evening with the Membership Mixer at 6 p.m., and continue the celebration at the Awards Banquet, Scholarship Recognition and Presidential Inauguration, where Robert J. Summerer, DO, 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 must be purchased in advance. To buy tickets and register for other annual meeting activities, visit sdmsa.org. Please purchase tickets and register by May 20.

Legal Brief Highlight: Reporting Elder Abuse

The law requires health care professionals to report suspected abuse or neglect of the elderly. Physicians and other health care professionals are required to file a report within 24 hours of reasonable cause to suspect abuse or neglect.

Suspected abuse must be reported to the state’s attorney of the county in which the elder or disabled adult resides, to the Department of Social Services, or to a law enforcement officer. Health care professionals who make such reports are granted immunity for doing so. Those who intentionally fail to make the required report are guilty of a Class 1 misdemeanor, punishable by up to one year in jail, a fine of $2,000, or both.

For more, download the SDSMA legal brief Elder Abuse at sdmsa.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 programs for members in the areas of practice management, leadership and health and wellness.
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