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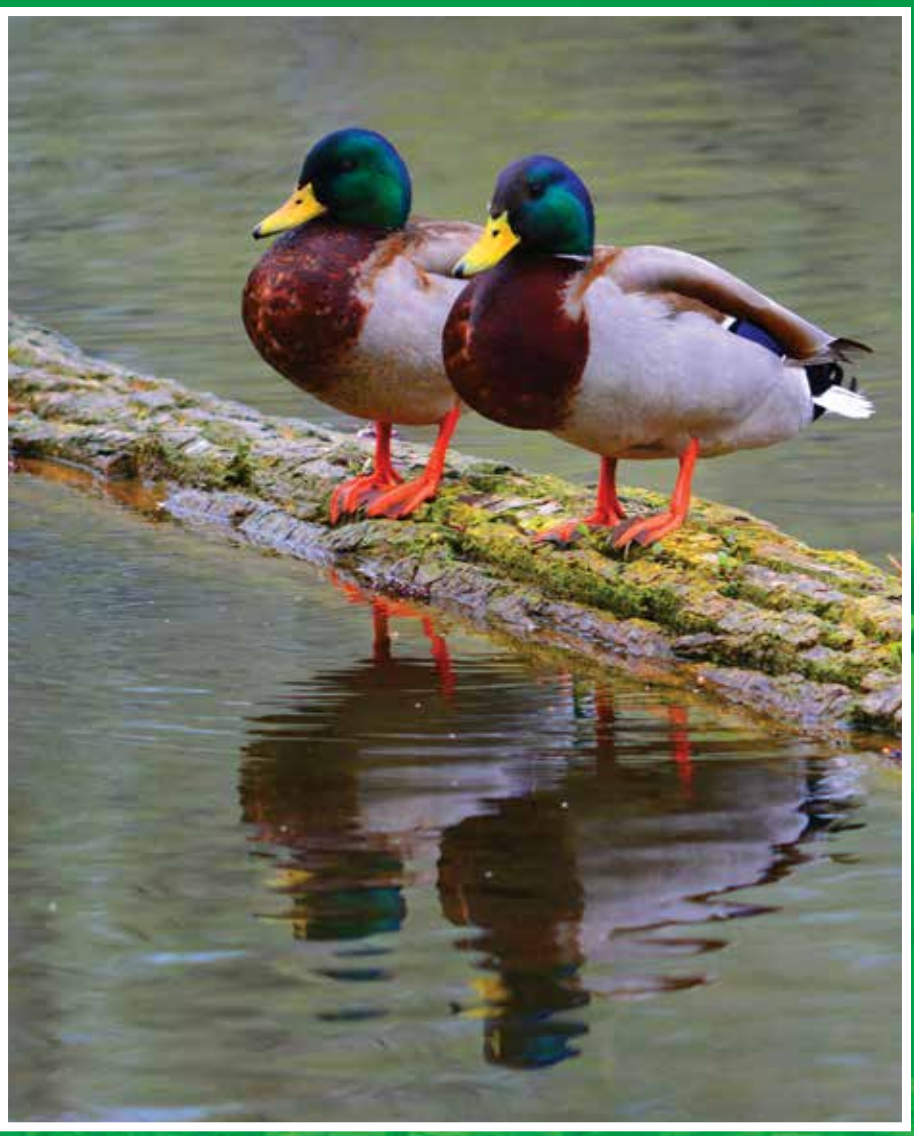

South Dakota medicine

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HOW TO PLAN YOUR DIGITAL LEGACY

ZACH DALLUGE CFP®, CKA® *Advisor*

As we come up on spring, many of us will be attending school concerts, sports competitions, and ultimately making memories. It wasn't long ago that you'd see parents with bulky camcorders and cameras with film that had to be developed to capture and preserve those memories. These days, almost everyone uses their phones to capture photos and videos, and it doesn't end there. More and more of our lives and assets are moving from tangible to digital.

When we discuss estate planning and leaving legacies to our heirs, we're usually talking about financial accounts and tangible property. We rarely think about digital assets. Digital Assets represent a wide range of property. They can include photos and videos, documents, cloud storage, email, social media accounts, cryptocurrency, and more. Some of those, such as cryptocurrency, have financial implications for your heirs. Others, such as photos and videos stored in the cloud may not have a financial impact but can be of considerable value to your heirs in preserving memories.

Currently, a single solution to preserve or pass on ownership of digital assets doesn't exist. This is where it becomes important to think about all of your digital assets and develop a plan for each. Here's how to go about it:

1. Create a list of accounts or other digital assets you'd like your heirs to have access to and how each can be accessed.
2. Research options, and develop a plan for each. For example, several of the major cloud and social media platforms allow you to name a contact to gain access to your data after you die. Both the terminology and requirements for that person vary by provider. For example, Apple and Facebook allow the designation of a "Legacy Contact", and Google allows you to name an "inactive account manager". For some data, you may not need to give access to on online service but, instead, store backups of digital assets on USB drives or other types of computer storage devices.

Several online services do not yet have the ability to add legacy contacts. For those services, it may make sense to use a password manager that has legacy features which allow a trusted person to have direct access to your online accounts after you pass.

Ultimately, the important thing is that you have a plan in place to pass on the assets you'd like your heirs to receive. While the digital asset category is broad and continues to grow, it is still in its infancy regarding how to deal with deceased individuals and requires a plan for each service.

At Foster Group, truly caring for our clients means taking the time to learn what's in their hearts and helping them pursue their goals. If you would like more information about planning your digital legacy, give us a call.

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Changing Policies in Medical Education and Public Health

Lucio N. Margallo II, MD
President, South Dakota State Medical Association

I graduated from medical school in 1970 after finishing two years, a bachelor of science (pre-med), four years of medical education proper, and one year of general rotating internship. My training and education moved on with three years of general surgery and three years of general internal medicine residency abroad and in the U.S.

To continue to improve high quality public health delivery, medical education and training are changing.

Medical education promotes a commitment to learning across the professional lifespan to ensure that physicians are prepared to respond to the country's changing health care needs. At both the national level and individual institutions, medical education is implementing innovations across the continuum of education and training to reflect the changing context of patient care, according to the Association of American Medical Colleges.

In 2015, 84 percent of medical school deans reported the need for specific admissions programs and policies designed to recruit a diverse student body, and the majority of respondents had established or expected programs/policies geared toward minorities underrepresented in medicine, students from disadvantaged backgrounds, and students from rural and underserved communities.

The changes in demographics, science and federal policies have had a major impact on the delivery of health care.

Medical institutions in the U.S. and the University of South Dakota Sanford School of Medicine implement strict criteria including high academic achievements, as well as the values and attitudes necessary to become excellent and compassionate physicians with a balance of experiences, attributes and academic metrics.

USD SSOM implements an award-winning curriculum and initiatives:

- Medical student research
- Transition to residency
- Medical decision making and evidence-based care
- Interpersonal education and care
- Dual degree programming
- Telemedicine and rural healthcare
- Art and humanities in medicine

The three pillar curriculum:

- Pillar 1 (System Block) – 18 months
- Pillar 2 Longitudinal Integrated Clerkship – 12 months
- Pillar 3 Sub internships, Rural Family Medicine, Surgery Subspecialties, Emergency Medicine, Professional Development, Transition to Residency – 16 months
- The school is in the 99th percentile for graduates who are practicing in rural areas
- The school was awarded a $13.5 million external research grant in 2021
- About 2,000 South Dakota physicians are involved in medical education

Given the demographic changes taking place across the U.S., it is great to see a commitment to developing a diverse and culturally competent student body.

Acknowledgements – Thank you to Tim Ridgway, MD, and Mark Beard, MD for providing information.

Preliminary Outcomes of the Pierre, South Dakota, Rural Residency Program

Mark K. Huntington, MD, PhD; and Teresa Bormann, MD

In 2012, the Governor's Primary Care Task Force developed recommendations for ensuring access to primary care for all the state's inhabitants. Among these recommendations was the development of additional primary care graduate medical education (GME) residencies in South Dakota.[1] Specifically, development of Family Medicine GME in a new, rural location was determined to offer a significant part of the solution to the state's needs and the Center for Family Medicine in Sioux Falls was contracted by the South Dakota Department of Health to develop and implement such a program.[2] The resulting program, the Pierre Rural Family Medicine Residency, received accreditation in Fall 2017 and the first class of interns matriculated the spring of 2018.[3] We present here a brief update on the residency program, with preliminary outcomes for graduates of the program.

Recruitment of resident physicians for the new program has been successful through the National Resident Match Program and its Supplemental Match. For the current (2023) entering class Match, there were 270 applications of whom approximately 40 were offered interviews for the two open positions.

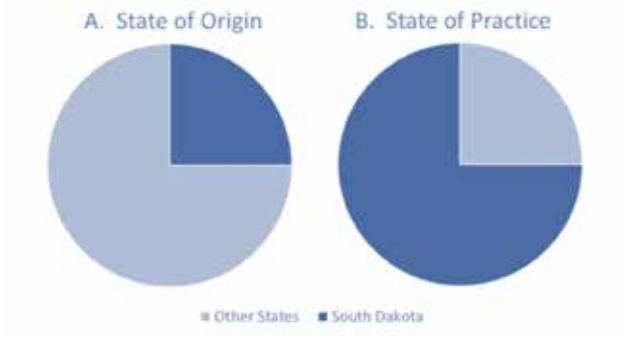
An early indicator of the efficacy of the program in placing physicians into rural practice is that 100% of the graduates of the Pierre residency's first two classes are in rural practice, 75% in rural South Dakota (Figure 1). This in-state placement of graduates increases to 83% when incorporating the upcoming graduating class of 2023, who have both signed contracts to practice in rural parts of the state upon graduation.

This high proportion of graduates retained in the state highlights that not only does the program attract physicians who will practice in rural areas, it also attracts physicians who specifically relocate and enter South Dakota medical practices. Three of these first four graduates were originally from other states; thus, there was a net gain of two physicians by the state as a direct result of the residency program.

In addition to practice location, academic quality is important. The program boasts a 100% first-attempt pass rate for the American Board of Family Physicians' specialty certification exam. While the ability to pass a written exam is distinct from clinical competence, it is an important indicator of quality.[4] As graduates of the program progress in their careers, other measures of physician quality are worth monitoring and comparing.[5]

Naturally, the Pierre Rural Family Medicine Residency Program has encountered a number of significant challenges, inherent to new programs, but these early signs suggest it has the potential to succeed in fulfilling its mission. It continues to evolve as a partner in the community while educating the state's future rural physician workforce.

Figure 1. State of origin and destination. (A) Graduates of the first two residency cohorts were predominantly from out-of-state. However, (B) the majority of graduates are practicing within South Dakota resulting in a net influx of physicians to the state, specifically rural regions.



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Alcohol-Related Death Rate Increasing at Alarming Rates

To the editor:

I want to highlight a toxic "epidemic" affecting our communities throughout the state at an alarming level; alcohol use disorder, also known as alcohol dependence, alcohol abuse or addiction. According to the National Institute of Health (NIH), it is characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational or health consequences. The factors that put one at high risk of alcohol use disorder (AUD) include drinking at an early age (less than 15 years), family history, and various mental health conditions, including depression.

When I moved to South Dakota a year and a half ago, I observed a significantly higher proportion of alcohol-related hospitalizations and mortality than I had experienced during my previous clinical experience in another state. It made me dig through the data summarized below.

According to a report published by the South Dakota Department of Health (SDDOH) in 2022, alcohol-related death rate increased by 107% during 2011-2020. Moreover, South Dakota had the sixth-highest crude rate for alcohol-related deaths in the U.S. during 2010-2019. The alcohol-related deaths (ARDs) can be acute from intoxication from alcohol or other drugs or due to longstanding complications from alcohol abuse. Lastly, the most common cause of alcohol-related deaths was due to alcoholic liver disease, as it accounted for 60%, and this has increased by 157% in the last 10 years.

The burden of this suffering is not limited to any particular section of the community. Still, it affects them differently, likely due to other socioeconomic and geographical factors affecting their access to healthcare. If we segregate ARDs by various subgroups, the rate of ARDs among males was double that of females. From 2011-2020, 57% of ARDs were whites, 40% were American Indian and 3% were other races. However, the American Indian population had a 7 times higher death rate than whites in our state during this period.

There has been a significant healthcare utilization from this preventable disease. According to the SDDOH report, alcohol-related hospitalization increased by 34% over the last five years, reaching 2,534 in the year 2020. The most common cause of alcohol-related hospitalization was alcohol dependence/abuse/use, accounting for 38% of these hospitalizations. 54% of the alcohol-related hospitalizations were whites, 39% were American Indian, and 8% were others.

I want to urge the leaders from the legislature, healthcare, colleges, community and religious groups to take the initiative to control this issue from getting worse. It is a need of the hour that we think about legislation for resource allocation, educating our adolescent population, restricting access to unsafe alcohol use in teens, and providing necessary psychiatric treatment resources to those with mental illness. Together, we can save lives. Additionally, we can significantly save healthcare spending on end-stage liver disease if we can prevent patients from falling prey to it in the first place. Increasing the number and consolidating the detox and alcohol rehab programs is another way to get these patients back to normalcy.

I am confident that with the sequence of realization, planning, implementation, and follow-up (RPIF), we can fight this urgent menace.

Muhammad Asif, MD

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Rural Land Management and Kidney Health

Shaopeng Gu, MS; Sydney Lovrien, MS IV; Mohammad Z. Qamar, MD; and Russell A. Wilke, MD, PhD

Abstract

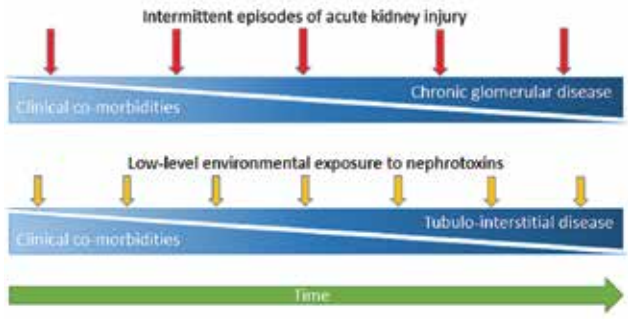
There is wide geographic variability in the prevalence of chronic kidney disease, and much of this variability is unexplained by known clinical risk determinants such as diabetes and hypertension. Additional factors contributing to this geographic variability include social determinants of kidney health, as well as genetic factors (ancestry) and non-genetic factors (the environment). Environmental nephrotoxins can accelerate the progression of kidney disease in some patients at risk. Examples of environmental nephrotoxins that have previously been associated with changes in glomerular filtration rate include chlorotriazine herbicides (e.g., atrazine) and trace metals (e.g., arsenic, cadmium, lead, and mercury). Land management practices influence the concentration of these nephrotoxins in our soil and water. In this review, we explore sustainable approaches to agriculture and the preservation of natural landscapes as land management practices that can optimize kidney health in a variety of communities.

Introduction

Worldwide, more than 1 in 10 adults have some form of chronic kidney disease (CKD), according to the National Kidney Foundation. In many cases, patients with kidney disease are unaware that they have a disorder.[1] CKD is an extremely heterogeneous phenotype, and guidelines published by the KDIGO organization (Kidney Disease Improving Global Outcomes) can be used to stratify this complex set of disorders based on differences in the pathophysiology and rate of progression.[2] CKD also varies widely according to geography.[3] In the U.S., administrative databases have been used to quantify regional variability in the prevalence of CKD. By geomapping claims data from over 50 million employees enrolled in a variety of fee-for-service and managed care plans, investigators from the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center recently characterized the distribution of CKD across all 50 states.[4] In general, these investigators observed lower CKD prevalence in the Northwest, and higher prevalence of CKD in the Southeast. Reasons for this variability are numerous and complex, and they range from social determinants of kidney health to a combination of clinical and environmental factors.[5]

Some forms of CKD are strongly influenced by air and water quality. A large proportion of the geographic variability in CKD cannot be explained solely by the presence of dysmetabolic traits (e.g., diabetes mellitus) and hemodynamic factors (e.g., hypertension).[6] While patients with chronic glomerular pathology often reflect well-characterized cardiometabolic risk determinants, patients with tubulo-interstitial pathology tend to develop disease from repeated exposure to nephrotoxic substances (Figure 1). In this context, nephrotoxicity can either be acute (as occurs with NSAIDs and antimicrobial agents) or chronic (as occurs with exposure to industrial and environmental pollutants). Acute interstitial nephritis (AIN) tends to spare the glomerulus, and it is estimated to account for 15-20% of all cases of acute kidney injury. Historically, however AIN is only reported in <3% of routine kidney biopsies.[7] This highlights the insidious nature of kidney disease due to nephrotoxins, and it underscores the paradox that tubulo-interstitial kidney injury is easily missed during routine lab testing involving the serum or the urine. Importantly, when this pattern of injury becomes repetitive and unrecognized, it can lead to fibrosis and infiltration of the renal parenchyma by lymphocytes, macrophages, and plasma cells, causing

Figure 1. Cumulative impact of physiologic and chemical stress leads to variability in renal pathology.



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irreversible and progressive decline in kidney function due to chronic interstitial nephritis (CIN).

Water quality is of considerable importance when assessing the potential causes of chronic tubulo-interstitial disease.[8] Water quality varies tremendously by geography. Public drinking water sources can differ in their chemical properties, reflecting the relative mixes of surface water and ground water that they are derived from. Ground water (from deep aquifers) and surface water (from large rivers) are managed locally by water treatment facilities to control factors such as sediment, microbial life, water hardness, and other chemical properties (oxidation potential). However, a large proportion of U.S. residents get their drinking water from non-public water supplies including private wells. Whether public or private, there is great variability in the chemical properties of the water obtained from these wells.

The United States Geologic Survey (USGS) keeps a detailed archive of the quality of water pumped from domestic wells. In 2009, the National Water Quality Program at USGS assessed conditions for more than 2,000 domestic wells across the U.S. [www.usgs.gov/node/96337]. The concentrations of major ions, trace elements, nutrients, radioactive compounds, and organic compounds (pesticides and volatile organic compounds) were measured, and concentrations were compared to Maximum Contaminant Levels (MCLs) set by the Environmental Protection Agency (EPA). These data are publicly available, and observational cohort studies are now being conducted linking physical location with individual patient medical records to generate risk prediction models for CKD based on geographic variability in exposure.[9]

Importance of Water Quality

In general, nephrotoxins can cause kidney injury through a variety of mechanisms.[10] These mechanisms include iatrogenic kidney injury (e.g., exposure to a vasoconstrictor in a patient who is volume contracted). Iatrogenic nephrotoxins can also cause podocyte injury (e.g., lithium), direct tubular toxicity (e.g., radiocontrast agents), or inflammation leading to interstitial nephritis (e.g., NSAIDs, proton pump inhibitors, and antibiotics). Patients exposed to *environmental nephrotoxins* may also develop forms of interstitial nephritis that can be either acute or chronic.

Most environmental nephrotoxins tend to lead to renal disease through prolonged exposure at low concentrations. Tubulo-interstitial injury from chronic exposure to environmental heavy metals, for example, can accelerate the progression of kidney disease due to other causes including the glomerular pathology associated with common dysmetabolic traits.[11] Severe tubulo-interstitial injury can also lead directly to CKD even in the absence of glomerular disease. A wide variety of environmental toxins can lead to interstitial nephritis, and it is often difficult to identify a causal agent; however, important clues may exist within the surrounding geography.

Potential nephrotoxins related to varied land management practices can range from silica to mycotoxins, and from heavy metals to synthetic organic compounds. Herbicides and pesticides represent one source of organic compounds capable of leading to kidney injury. Data from the Agricultural Health Study (AHS), for instance, have documented an increased rate of end-stage renal disease (ESRD) in licensed pesticide applicators.[12] More recently, analyses using estimated glomerular filtration rate (eGFR) as a continuous trait in a subcohort of the AHS population have revealed decreased renal function in agricultural workers who specifically applied herbicides such as atrazine (-3.7% lower eGFR), dicamba (-2.8% lower eGFR), or pendimethalin (-3.7% lower eGFR), when compared to agricultural workers that never used those herbicides.[13] Multivariate models considering the presence or absence of clinical comorbidities in that cohort have subsequently confirmed an association between atrazine and CKD as a binary trait.[13]

USGS water quality data are used to record the concentration of chlorotriazines like atrazine in water from public wells. Table 1 shows the concentrations of various herbicides measured in these public wells between 1993 and 2007.[14] Agricultural chemicals are found quite commonly in these wells. As shown below, atrazine and simazine were detected in 26.6% and 14.3% of the wells sampled (total chlorotriazines were detected in 33.1% of the wells). This class of herbicides interferes with photosynthesis in broadleaf weeds as well as in some select grasses. Atrazine is largely a pre-emergent herbicide, which means that it is typically applied before weeds have surfaced. It remains active in the soil for approximately six weeks. Eventually, these chlorotriazine herbicides undergo physical, chemical, and biological degradation in the soil. A healthy soil – with good structure and adequate pore size to support rapid rainwater infiltration and diverse microbiota – is therefore needed to keep these compounds out of our drinking water.

Heavy metals are another class of environmental nephrotoxins known to vary with geography and soil conditions. Non-essential polyvalent cations like arsenic, cadmium, and lead can access the human body through inhalation, ingestion, or transdermal absorption. Chronic

Table 1. Number of detections and summary statistics (i.e., percentile concentrations in µg/L) for agricultural chemicals measured in U.S. public-well samples collected during 1993–2007. Reprinted from USGS.

Contaminant	Number of samples	Number of detections	Detection frequency (percent)	Percentile concentrations (µg/L)					Maximum detected concentration
				50th (median)	75th	90th	95th	99th	
Pesticide compounds									
Alachlor	869	16	1.8	<0.003	<0.003	<0.003	<0.003	0.011	0.249
Atrazine	853	227	26.6	<0.004	0.003	0.017	0.037	0.19	1.23
Bentazon	589	16	2.7	0.005	0.006	0.007	0.010	0.011	0.491
Bromacil	590	30	5.1	0.004	0.006	0.011	0.026	0.091	1.079
Carbofuran	644	13	2.0	<0.01	<0.01	<0.01	<0.01	0.013	0.17
p,p'-DDE	512	14	2.7	0.001	0.001	0.001	0.001	0.002	0.004
Deethylatrazine	853	257	30.1	0.002	0.004	0.014	0.035	0.11	0.346
Dieldrin	896	28	3.1	<0.004	<0.004	<0.004	<0.004	0.038	0.106
Diuron	587	31	5.3	0.005	0.006	0.010	0.018	0.16	0.3
Fenuron	587	6	1.0	0.004	0.004	0.004	0.004	0.03	0.067
Fluometuron	590	6	1.0	0.007	0.007	0.007	0.007	0.021	1.22
Metolachlor	870	75	8.6	0.001	0.001	0.003	0.005	0.064	3.58
Metribuzin	898	11	1.2	<0.014	<0.014	<0.014	<0.014	0.007	0.105
Norflurazon	585	6	1.0	<0.077	<0.077	<0.077	<0.077	0.019	0.069
Prometon	885	93	10.5	0.001	0.001	0.005	0.008	0.022	0.244
Simazine	884	126	14.3	0.002	0.002	0.005	0.012	0.067	0.315
Tebuthiuron	859	40	4.7	0.007	0.007	0.007	0.007	0.031	1.44
Total chlorotriazines	886	293	33.1	0.004	0.009	0.043	0.091	0.34	1.576

Available at http://pubs.usgs.gov/sir/2010/5024/pdf/sir20105024.pdf.
DDE (dichloro-diphenyl-dichloroethylene) a persistent breakdown product of DDT (dichloro-diphenyl-trichloroethane).

cumulative exposure to these heavy metals is therefore largely dependent upon ambient air quality and the chemical properties of surrounding water sources. While heavy metals occur naturally, they are rarely found at levels high enough to influence human health; however, exposure can vary in accordance with land management practices. For example, agricultural soil near mineral extraction mines can contain elevated levels of copper, zinc, arsenic, cadmium, and lead,[15] and soil erosion can move these heavy metals into the surface water and ground water.[16] Erosion due to deforestation can also mobilize heavy metals.[17] In biomes where soil erosion is severe, surface water concentrations of these metals can often exceed international guidelines.[18]

Risk for CKD from heavy metal exposure is therefore dependent on land management and local water quality. In the U.S., data from NHANES (a program of studies designed to assess the health and nutritional status of adults and children in the U.S.) indicate that exposure to low levels of arsenic, cadmium, lead, and/or mercury early in life can influence the development of renal dysfunction in adulthood.[19] For arsenic, data from the Strong Heart Study (a cross-sectional analysis of adults in the western U.S.) have revealed an association between urinary metabolite levels and CKD in Native Americans.[20] Once ingested, inorganic arsenic is methylated to produce monomethyl-arsenic (MMA) and dimethyl-arsenic (DMA). Both MMA and DMA have been associated with CKD (adjusted Odds ratio: 3.8 and 1.8, respectively) in this cohort.[20]

Arsenic is quite frequently identified in well samples recorded by the USGS. Table 2 shows the concentrations for trace elements in public-well sampled during 1993-2007, compared to EPA benchmarks.[14] As illustrated, arsenic was found above the EPA threshold in 9.9% of all samples.

Elevated arsenic levels are found at an even higher frequency in some communities outside the U.S. In the Andes Mountains of South America, arsenic is released from the volcanic bedrock into the groundwater. Pre-Columbian mining activities near what is now the Argentinean village of San Antonio de los Cobres have left a legacy of high arsenic levels within the local drinking water.[21] Genomic studies in that community have indicated that a subset of individuals residing in the region are at higher risk of developing CKD specifically within the context of increased arsenic exposure. In a genome-wide association study (GWAS) conducted with 124 unrelated individuals who had been phenotyped for urinary levels of MMA and DMA in that community, the gene locus most strongly associated with urinary arsenic levels was *AS3MT* (encoding an arsenite methyltransferase).[21] This same locus was also associated with urinary arsenic levels in a subset of 1,313 individuals from the HEALS cohort (Health Effects of Arsenic Longitudinal Study), a prospective study of health outcomes linked to arsenic exposure in rural Bangladesh.[22]

Table 2. Number of detections and comparison of concentrations to human-health benchmarks for representative metals measured in U.S. public-well samples collected during 1993–2007.

Trace element	Number of samples	Number of detections	Human-health benchmark[1]		Samples with BQ>1		Samples with BQ>0.1 and ≤1	
			Value (µg/L)	Type	Number	Percent	Number	Percent
Aluminum	598	299	–	–	–	–	–	–
Antimony	619	105	6	MCL	1	0.2	5	0.8
Arsenic	638	444	10	MCL	63	9.9	206	32.3
Barium	630	627	2,000	MCL	1	0.2	49	7.8
Beryllium	622	37	4	MCL	0	0	1	0.2
Boron	501	497	1,000	HBSL	14	2.8	126	25.1
Cadmium	631	109	5	MCL	0	0	1	0.2
Chromium	626	309	100	MCL	0	0	13	2.1
Cobalt	627	396	–	–	–	–	–	–
Copper	625	497	1,300	MCL[2]	0	0	0	0
Iron	809	449	–	–	–	–	–	–
Lead	630	348	15	MCL[2]	3	0.5	70	11.1
Lithium	458	448	–	–	–	–	–	–
Manganese	808	543	300	HBSL	37	4.6	125	15.5
Molybdenum	628	485	40	HBSL	4	0.6	131	20.9
Nickel	629	444	100	HBSL	0	0	7	1.1
Selenium	632	299	50	MCL	1	0.2	17	2.7
Silver	606	4	100	HBSL	0	0	0	0
Strontium	503	503	4,000	HBSL	15	3.0	231	45.9
Thallium	437	93	2	MCL	0	0	5	1.1
Uranium	650	467	30	MCL	5	0.8	148	22.8
Vanadium	457	404	–	–	–	–	–	–
Zinc	613	561	2,000	HBSL	1	0.2	5	0.8
All analyzed trace elements	*810*	*787*	*various*	*various*	*133*	*16.4*	*458*	*56.5*

Reprinted from USGS. Available at http://pubs.usgs.gov/sir/2010/5024/pdf/sir20105024.pdf.
Human health benchmarks1 include MCL (Maximum contaminant level established by the U.S. Environmental Protection Agency)2,
and HBSL (health-based screening level calculated by the USGS in conjunction with the U.S. Environmental Protection Agency) [http://pubs.usgs.gov/sir/2007/5106/section2.html]. BQ = Benchmark quotient (ratio of concentration to human health benchmark).

Additional toxicogenomic predictors of risk are also emerging in the context of occupational exposure. During the process of gold mining, for example, elemental mercury (Hg^0) is used to recover gold through amalgamation. When the amalgam is heated, mercury vapors can be inhaled and Hg^0 is then converted to inorganic mercury (Hg^{1+} or Hg^{2+}) which is conjugated to glutathione and excreted into the proximal tubules. In a cohort of 160 gold miners, variants in glutathione-related candidate genes have recently been associated with mercury-induced kidney damage.[21] Despite modest sample size, these analyses identified a gene interaction linking glutathione synthetase (*GSS*) and a glutathione-S-transferase (*GSTA1*) with higher urinary levels of mercury ($p = 0.04$), and a single variant in the catalytic subunit of glutamate-cysteine ligase (*GCLC*) was strongly associated with tubular injury as determined by urinary levels of beta-2-microglobulin ($p = 0.02$). For the latter association, the effect size was quite large (β coefficient = −19.32), and the gene variant was very common (minor allele frequency = 0.36).[23] Thus, two important principles are emerging as our understanding of environmental nephrotoxicity deepens: (1) genetic variability in some phase II detoxifying enzymes (e.g., glutathione-transferases and methyltransferases) are key contributors to CKD risk, and (2) the overall risk reflects a combination of genetic predisposition and environmental exposure.

Geographic Variability in Exposure

In principle, residential and/or occupational exposure to environmental contaminants can occur through inhalation, ingestion, or transdermal absorption. Air pollution, for example, can serve as a source of residential inhalational exposure, and it can also serve as a mechanism for the dispersal of particulate matter containing toxicants that eventually enter the ground water and surface water. Suspended particulate matter often contains a mix of organic and inorganic nephrotoxins (including heavy metals). Particulate matter less than 10µm in diameter (PM_{10}) can get

Let's get to the root of the problem

As providers, we know that substance misuse and addiction are often just symptoms of more complex problems. For treatment to be effective, the whole person—their basic needs, mental health, physical conditions, and overall safety must be addressed.

Talking with your patients is a great place to start—helping them find a support team is even better. The Resource Hotline can provide your patients with the services and support they need to fully recover including:

- Connecting to housing, employment, and food assistance
- Help accessing treatment and recovery services
- Identifying financial assistance opportunities
- Parenting education
- Follow up services with a personal guide for addiction recovery through the Care Coordination program

Your guidance is powerful. Patients are more likely to follow through when you recommend a course of action.

Refer your patients and their families to the

Resource Hotline
1-800-920-4343

It's FREE, confidential, and available 24/7.

Together, we can treat the whole person and set them on the path to recovery.

AvoidOpioidSD.com/find-help

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inhaled deep into the lungs, and particles less than 2.5µm in diameter ($PM_{2.5}$) can cross the pulmonary epithelium to access the systemic circulation. Fine particulate matter not only influences hospitalization rates for lung disease, it also hastens the progression of disease within other organs ranging from the kidneys to the brain.[24] Using a satellite-based, spatiotemporal model representing 47,204 adults from the China National Survey of CKD, investigators at Peking University recently observed that an increase of 10µg/m^3 in ambient $PM_{2.5}$ is associated with an increased prevalence of CKD (odds ratio 1.28; 95% CI 1.22 to 1.35) as well as an increase in the frequency of albuminuria (odds ratio 1.39; 95% CI 1.32 to 1.47).[25]

In the western U.S., exposure to atmospheric particulate matter is greater in counties with large agricultural populations.[26] This can be partly reduced through erosion control. Investigators in Canada for example have observed a 47% reduction of $PM_{2.5}$ over several decades, when minimum tillage and cover cropping strategies were implemented between 1981 and 2006.[27] This reduction of atmospheric particulate matter can produce significant impact on exposure to environmental nephrotoxins. Cadmium, for instance, is a known component of suspended particulate matter. In farming communities close to the equator, chronic interstitial nephritis is quite common,[28,29] and heavy metals such as cadmium, lead, and mercury have been detected at levels above allowable limits in biological samples obtained from farm workers residing in these communities.[30] As shown in Table 2, some metals are commonly found in public wells sampled across the U.S. Arsenic for example is present at subthreshold levels in nearly 1 in 3 public wells surveyed by the USGS.[31] The distribution of arsenic levels is shown in Figure 2. This image represents a high-level survey of arsenic concentration determined in 62 principal aquifers located across the U.S. Data for many more ground water aquifers are available at the regional and local levels. In South Dakota, for example, the USGS National Water Information System water-quality database has been used to characterize the water quality of aquifers in the Black Hills area [http://pubs.usgs.gov/wri/wri014194/].[32] In this report, ground water characteristics are presented for more than 12 aquifers in western South Dakota alone (i.e., the Precambrian aquifer, as well as the Deadwood, Inyan-Kara, Madison, Minnekahta, Minnelusa, Morrison, Pierre, Graneros, Newcastle, Spearfish, and Sundance aquifers). Mean arsenic concentration in ground water sampled from the Precambrian aquifer was 4.2 mg/L (range <0.5 to 103 mg/L, from n = 52 samples), and 4 of the 52 wells sampled within this aquifer had arsenic concentrations exceeding the maximum contaminant level (MCL) of 10 mg/L established by the EPA.

Figure 2. Distribution of mean arsenic concentration in public wells.

Reprinted from USGS. Available at http://www.usgs.gov/mission-areas/water-resources/science/arsenic-and-drinking-water#overview.

Whether inhaled as particulate matter or orally ingested and absorbed across the gastrointestinal mucosa, once these metals access the systemic circulation they are passively filtered by the kidneys at the level of the glomerulus. They are also actively transported into the renal tubules (via organic cation transporters and toxin extrusion proteins). In the context of chronic low-level exposure, endocytosis can facilitate the movement of these metal-protein complexes into tubular epithelial cells at concentrations capable of overwhelming oxidative defense mechanisms. This process slowly and insidiously leads to CKD over time. For example, in patients with a high total body burden of cadmium, longitudinal measurements of urinary cadmium levels have revealed that its elimination half-life ($t_{1/2}$) can exceed 10 years.[33]

In any attempt to reduce exposure to a nephrotoxin, it is important to distinguish between inhalational exposure and exposure by ingestion of contaminated water or food. *Non-point sources of pollution* (e.g., atmospheric contaminants) can lead to both. Deposition of toxicants onto the land surface can lead to significant drinking water contamination, particularly if the toxicants move through the soil into ground water aquifers. Conversely, *point source pollutants* (e.g., from sewage treatment plants, oil refineries, paper mills, factories, and farms) can access surface water directly through erosion and run-off. Point source pollutants can also

access the ground water if they are not sequestered and/or decontaminated within the soil. Fortunately, this problem can be greatly reduced through the optimization of land management practices.

Role of Land Management

In general, the ability of environmental contaminants to enter our water supply is strongly influenced by the physical and chemical properties of the soil. Soil structure and pore size are important because they impact water infiltration rates and mitigate against erosion and run-off. Soil pH and water hardness are also key properties that impact the mobilization of toxicants. Regional differences in water hardness (i.e., the concentration of polyvalent metal cations like calcium, magnesium, and iron) can influence the onset and rate of progression for CKD.[34] This correlation is partly attributable to the impact of water hardness on the mobility of nephrotoxic metals. At high pH, naturally occurring metals like cadmium tend to precipitate as hydroxides or carbonates. As the pH decreases, however, precipitation becomes less important and cation exchange (hardness) becomes an important determinant of heavy metal mobility.[15,34]

Healthy soil also detoxifies organic and inorganic environmental contaminants. The $t_{1/2}$ of many commonly used agricultural chemicals (e.g., herbicides and pesticides) are much lower in the soil than in surface water or ground water. Glyphosate for example has a $t_{1/2}$ of 100 days within ground water, but its $t_{1/2}$ is reduced to 50% of that value in a healthy soil.[35] Synthetic fertilizers undergo a similar fate. Soil with no structure allows inorganic nitrogen-containing fertilizers (e.g., NH_4^+, NO_2^-, NO_3^-) to run-off into the surface water. Alternatively, mature soil is deep enough and structurally complex enough to minimize the leaching of inorganic fertilizers and other potential toxicants into ground water.[36] Water contamination is therefore avoidable, and sustainable approaches to land management will play a key role in reducing the burden of CKD.

Changes in tillage strategy and crop diversity, for example, are already being leveraged to decrease the runoff migration of environmental toxicants into surface waters.[37,38] Another promising approach has been *regenerative agriculture* (Box 1) – an intentional effort to preserve soil structure by integrating cropland with planned rotational grazing.[36] The principles of regenerative agriculture maintain soil structure with adequate pore size and robust microbiota. These practices deepen the soil, maximize the rate of water infiltration, and minimize the ability of environmental toxicants (from a variety of industries) to access our air and drinking water.

Box 1. Principles of regenerative agriculture

Minimize soil disturbance
minimize tillage
minimize pesticides
preserve soil structure
overall benefit: increased pore size; optimization of water infiltration rates

Maximize cover crops
maintain crop diversity
emphasize living roots
keep soil covered year round
overall benefit: storage of nitrogen; and microorganisms cycle more carbon

Integrate livestock
maintain animal diversity
controlled grazing to stimulate root growth
rotational grazing to increase soil organic matter
overall benefit: expansion of structure; more carbon stored below-ground

To effectively control soil erosion and reduce the run-off of environmental pollutants impacting human health, these principles need to be adjusted regionally.[39] Winter cover crops, for example, vary in their ability to contribute root mass and generate long-term resistant soil organic matter. In South Dakota, wheat is a major cover crop, and approximately half of the 1 million-plus acres of total wheat planted in this state are planted as winter wheat (http://extension.sdstate.edu/effects-snow-wheat). The reason is related to the amount of snowpack. Other crops like corn and soybeans can be damaged in this region due to variability in snow depth and cold temperatures. When seeded late in the growing season, winter wheat establishes dense root mass and becomes gradually acclimatized before going dormant during the hard winters of the Northern Plains. This leads to healthy soil capable of filtering and detoxifying environmental pollutants before they gain access to our water resources. The community then benefits from improved water quality.

Efforts to maintain *natural landscapes* (including forest, prairie and wetland habitat) also lead to improved water quality.[40-42] Within the U.S., the Conservation Reserve Program (CRP) has been implemented to expand these landscapes, and to reduce the runoff of non-point source pollutants (http://www.fsa.usda.gov/programs-and-services/conservation-programs/conservation-reserve-program/index). Examples of targeted enrollment initiatives have included pollinator habitat, upland bird habitat, prairie waterfowl habitat and

floodplain wetlands restoration, as well as the *state acres for wildlife enhancement* (SAFE) program and the *highly erodible land initiative* (HELI). Upcoming pilot programs include prolonged sign up for the *soil health and income protection program* (SHIPP) which incentivizes producers to plant vegetative cover on less productive croplands for three to five years. Clearly, CRP improves both air and water quality,[40,41] and in 2022, the total amount of U.S. land committed to these programs exceeds 22 million acres.

Currently there are 8 billion people living on earth. This doubling of the world's population over the past 50 years has created an unprecedented global demand for food. To meet this demand, the people that produce our food are placing increased emphasis on sustainable approaches to land management. These approaches will continue to nurture the soils that filter and detoxify our water and air. As the world moves increasingly toward regenerative agriculture and preservation of natural landscapes, we are presented with a tremendous opportunity to reduce the overall burden of disease for conditions known to be influenced by air and water quality. Because of the potential adverse impact of environmental toxicants on the rate of progression for kidney disease, the optimization of land management will improve kidney health in the patients that we serve.

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SOUTH DAKOTA

Childhood Lead Poisoning Prevention Program

The South Dakota Childhood Lead Poisoning Program (SD CLPPP) screening and testing guidelines have been approved by the South Dakota Lead Advisory Group.

The SD CLPPP recognizes there is **NO safe level of lead in the blood** and recommends that South Dakota health care providers screen all children for the risk of lead exposure at 6, 9, 12, 18, & 24 months, and at 3, 4, 5, and 6 years of age during well child visits. These recommendations align with the American Academy of Pediatrics Bright Futures guidelines.

Testing Recommendations for Certain Populations

Medicaid

The Centers for Medicare and Medicaid Services (CMS) recommends for Medicaid-enrolled children:

- Blood lead level testing (either capillary or venous) should be performed at 12 and 24 months of age.
- Children 36–72 months who missed recommended testing at a younger age should be tested.

Immigrants, Refugees, and Foreign Adoptees

The Centers for Disease Control and Prevention (CDC) recommends initial testing for the following:

- All infants and children ≤16 years of age
- Adolescents >16 years of age if there is a high index of suspicion, or clinical signs/symptoms of lead exposure.
- All pregnant and lactating women and girls

Follow-up testing with blood test, 3-6 months after initial testing:

- All infants and children ≤6 years of age, regardless of initial screening result
- Children, adolescents, and pregnant or lactating women who had a blood lead result ≥3.5µg/dL.

Find more information at DOH.SD.GOV/BloodLead/

RECALLED ITEMS

A list of recalled items is found on the Consumer Product Safety Commission website because they contain paint that has levels of lead that exceed the federal lead paint ban, posing a health hazard. https://www.cpsc.gov/

RISK ASSESSMENT

The risk assessment questions can be used for screening during pediatric care visits to help identify exposures to lead. It is recommended to conduct lead testing using a capillary or venous specimen if the answer to any question on the Verbal Risk Assessment is "Yes" or "I don't know.

Scan to take the Risk Assessment

CONTACTS

Call 605-773-3737 for questions regarding case management of children with lead in blood

Fax results to 605-773-5509, using the secure website: sd.gov/diseasereport, or by mail to: Infectious Disease Surveillance, Department of Health, 615 East 4th Street, Pierre, SD 57501; marked "Confidential Disease Report"

CHILDHOOD Lead POISONING PREVENTION PROGRAM

SOUTH DAKOTA DEPARTMENT OF HEALTH

Angioinvasive Fungal Thyroidits

Andrew Holmes, MS III; Brendan Wechsler, MD; and Douglas Lynch, MD

Abstract

Fungal thyroiditis is an uncommon cause of thyroid inflammation and infection. This condition is typically observed within immunosuppressed patients, such as those with a hematologic malignancy or those receiving corticosteroids or chemo-radiation therapies. This report describes a case of a 66-year-old male with underlying high-risk myelodysplastic syndrome who presents with complaints of fever, right anterior neck pain, severe dysphagia, dysphonia, and difficulty managing upper airway secretions. A cervical computed tomography scan was performed and depicted a low-density area within the right thyroid lobe, infiltration of adjacent anterior fat tissue, and a retropharyngeal fluid collection. Ultrasound-guided biopsy and cytology revealed pauci-septate fungal hyphae with vascular invasion and abundant necrosis which is consistent with a diagnosis of angioinvasive fungal thyroiditis. This case demonstrates the importance of considering fungal species as a potential etiology in immunosuppressed patients with acute development of thyroiditis.

Introduction

Inflammation of the thyroid gland, also known as thyroiditis, may occur due to autoimmune disease, infectious processes, pharmacologic agents, or fibrotic processes.[1] Various classifications exist for thyroiditis based on the presentation of symptoms and etiology, and it may manifest as hypothyroidism and/or hyperthyroidism in a fleeting or permanent nature. Although autoimmune disease is the most common etiological process of thyroiditis, infectious agents such as bacteria, viruses, and fungi may cause thyroid gland inflammation.[1] Fungal thyroiditis is less commonly observed than bacterial thyroiditis in patients, often discovered incidentally through antemortem radiographic imaging with subsequent biopsy or at autopsy in immunosuppressed patients with disseminated fungal infection.[2,3] Although symptoms and signs of fungal thyroiditis may not be present, clinical symptoms may include neck pain, fever, dysphagia, odynophagia, and neck erythema with evidence of hypothyroidism or hyperthyroidism.[2,3] High clinical suspicion for fungal thyroiditis is warranted in patients exhibiting the aforementioned symptoms paired with hematologic malignancies or immunosuppressive therapies like corticosteroids or chemotherapy and radiation.[2,3] Depending on the case severity, treatment warrants antifungals and surgical intervention which may include drainage or thyroidectomy.

Case Report

The patient is a 66-year-old male with recent past medical history including a prolonged two-month hospitalization for small bowel obstruction complicated by the diagnosis of high-risk myelodysplastic syndrome and hospital-acquired pneumonia, with noted physical deconditioning during the hospital stay. He was briefly discharged to a rehabilitation facility and there was noted improvement in his physical function, but he was re-hospitalized due to development of scrotal abscess following initiation of decitabine on Jan. 11 through Jan. 15, 2019. The patient's left hemiscrotum was noted to have expressible, purulent drainage of a 6 cm x 6 cm fluctuant, indurated, and erythematous area without signs of crepitus or necrosis. The scrotal abscess was incised, drained, and sample sent for culture with Gram stain and sensitivity. The patient was started on empiric piperacillin-tazobactam until cultures revealed primarily Gram negative rods consistent with *Psueodomonas aeruginosa* and some *Candida albicans*, and he was promptly switched to ciprofloxacin. He received a delayed second dose of chemotherapy on Feb. 27 through March 3, 2019 due to prior infectious complications. The patient presented following his second round of chemotherapy treatment on March 4, 2019 with neutropenic fever and pancytopenia.

On presentation he was severely deconditioned and malnourished despite, with spiking fevers up to 102 degrees F. Physical examination was overall unrevealing with no localizing symptoms or signs of infection, and the prior scrotal wound was healing well without evidence of further infection. The patient's neck was supple without adenopathy; heart auscultation revealed a normal rate, regular rhythm, and no abnormal sounds; the lungs had decreased breath sounds without wheezing or crackles; abdominal examination did

not reveal abnormal sounds or masses, although the patient had tenderness near his gastric tube; the skin had normal color and turgor without suspicious rashes or other lesions. Laboratory results on admission revealed a WBC count of 2.0 K/mL (4.0-11.0 x 10^3 U/mL), hemoglobin of 5.9 g/dL (13.0-18.0 g/dL), and a platelet count of 84 K/mL (140-400 K/mL). Absolute band count was elevated at 0.9 K/mL (0-0.7 K/mL) with an absolute neutrophil count of 700/uL. Measurements of alkaline phosphatase was 208U/L (38-126 U/L), alanine aminotransferase was 90 U/L (0-50 U/L), serum total protein was 4.6 g/dL (6.3-8.2 g/dL), and lactic acid was 2.2 mmol/L (0.3-2. 1mmol/L). He began empiric antibiotic treatment including ampicillin-sulbactam for fever of uncertain source and was later transitioned to Vancomycin for concerns of possible gastric-tube site infection. He remained afebrile on this treatment from March 5 until March 17, when nursing staff noted a bout of emesis followed by respiratory distress and issues with respiratory clearance.

A computed tomography angiography (CTA) of the chest was performed on March 17 for acute concerns of pulmonary embolus versus aspiration pneumonia which showed no emboli. The study depicted enlarging bilateral pleural effusions compared to a CTA two weeks prior, as well as an enlarged thyroid gland unchanged from prior studies with otherwise normal thoracic inlet structures (Figure 1). He was treated for concerns of aspiration pneumonia at this time with IV cefepime following sensitivity testing on sputum cultures which grew Citrobacter freundii and Candida albicans. Intravenous antibiotics were discontinued upon diagnosis of Clostridium difficile colitis on March 21 with abdominal pain and multiple watery bowel movements daily, for which he began treatment with oral vancomycin.

On March 25 a rapid response code was called due to acute complaints of fevers, right anterior neck pain, severe dysphagia, and issues managing upper airway secretions. The patient denied any respiratory concerns aside from excess secretions and hoarseness of voice. Vitals at the time were significant for temperature of 101.4 degrees F, blood pressure of 129/72, heart rate of 118, and respiratory rate of 56 breaths/minute on 5 liters via oxygen mask. A computed tomography (CT) of the cervical soft tissues was performed, revealing a nodular area of low density involving the right thyroid lobe measuring 3x2x3 cm in dimension, medial deviation of the right vocal cord, fatty infiltration of the adjacent anterior neck tissue, and retropharyngeal fluid collection (Figure 2). An ultrasound-guided biopsy of this nodule on March 26 demonstrated a 2.1x1.8 cm hypodense lesion within the superior right thyroid gland corresponding to the abnormality seen on CT (Figure 3). Culture and Gram stain of the aspiration did not yield any identifiable bacterial organisms. Further pathology analysis revealed abundant necrosis with branching pauci-septate fungal hyphae with presence of vascular invasion consistent with a diagnosis of angioinvasive fungal thyroiditis (Figure 4). Due to worsening clinical status and severity of comorbid medical conditions, a joint decision was made with the patient and family to forego systemic antifungal therapy and transition to comfort care. The patient expired the following day.

Figure 1. Computed tomography angiogram depicting homogenous, normal appearing thyroid tissue (yellow arrows) without evidence of thyroiditis two weeks prior to onset of symptoms.

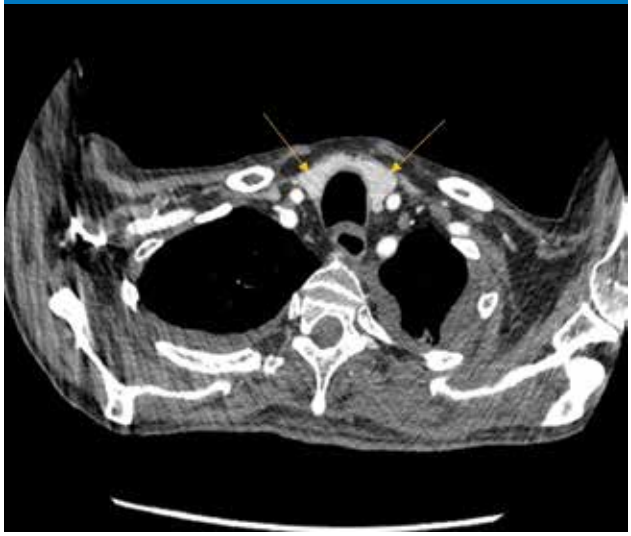


Figure 2. Computed tomography of the neck denoting low-density areas (yellow arrows) of the right thyroid gland lobe and inferior left lobe.

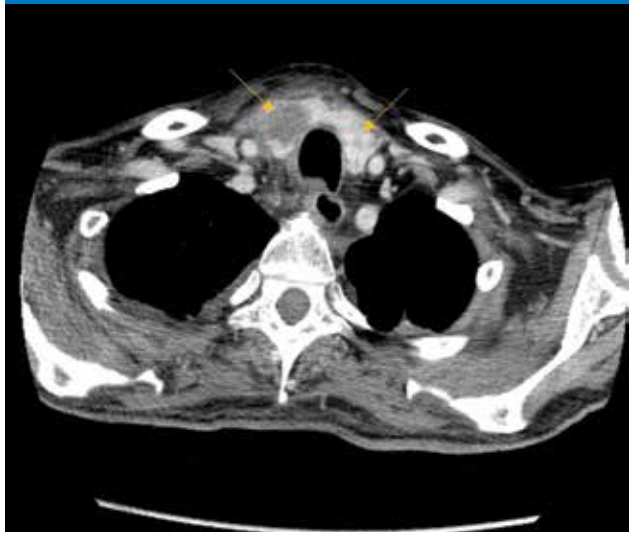


Figure 3. Ultrasound images obtained prior to ultrasound-guided needle biopsy of hypoechoic area in right thyroid lobe.

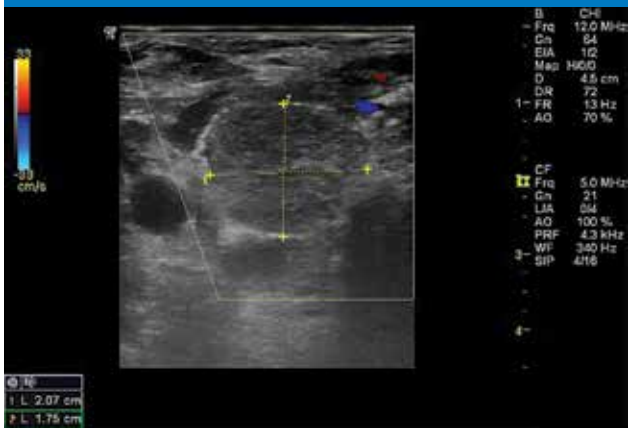
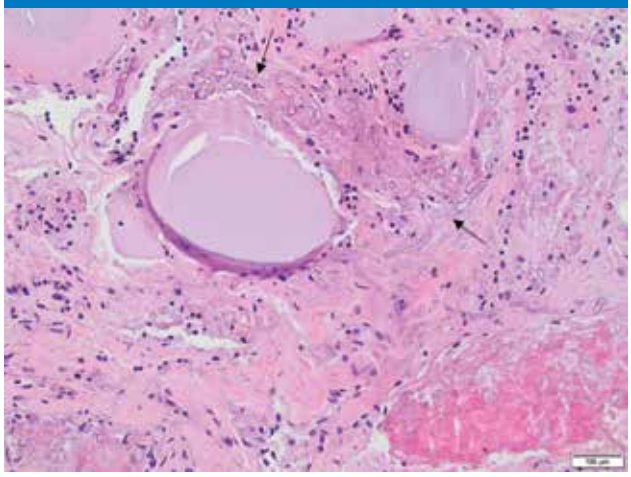


Figure 4. Histological section (200X magnification) demonstrating abundant necrosis with branching pauci-septate fungal hyphae (black arrows) with invasion into the vasculature and parenchyma.



Discussion

Infectious thyroiditis is caused by a non-tuberculoid bacterial species in 65% of cases, tuberculous species in 25% of cases, fungal species in 9% cases, and a parasite in 1% of cases.[3] Tuberculous thyroiditis is typically observed in patients living in areas where tuberculoid species are endemic.[3] Fungal thyroiditis is a quite rare cause of thyroid infection, and almost all cases are observed in immunosuppressed patients with disseminated fungal disease.[2,3] Patients at increased risk for invasive fungal infection of the thyroid include those with hematologic malignancies, organ-transplant recipients, individuals receiving immunosuppressive pharmacotherapy, chemotherapy or radiation, patients with human immunodeficiency virus, and those with autoimmune diseases.[2,3] Infectious etiologies of thyroiditis are rare due to innate protective mechanisms: extensive vascular and lymphatic network, fibrous capsules encompassing the gland, and fascia planes separating the thyroid from other cervical structures.[2]

Documented cases of fungal thyroiditis include *Aspergillus* species, *Coccidioides immitis*, *Blastomyces* species, *Histoplasma capsulatum*, *Scedosporium* species, *Pseudallescheria boydii*, and *Cryptococcus neoformans*.[2,3] *Aspergillus* species has been the most reported cause of fungal thyroiditis.[2,3] Our case adds another documented report of thyroiditis due to a fungal species. Although fungal thyroiditis is the second most common cause of infectious thyroid inflammation behind bacterial thyroiditis, patients with fungal thyroiditis have a higher mortality rate likely due to other comorbidities and their already immunosuppressed state.[1-3]

Signs and symptoms of fungal thyroiditis include goiter with potential for dysphonia and dysphagia, anterior cervical pain, fever, and evidence of hypo or hyperthyroidism on clinical and laboratory assessments.[2,3] If there is suspicion for infectious thyroiditis, patients are suggested to receive broad-spectrum antibiotics to cover the most common bacterial etiology; antifungals may be added if the patient is immunosuppressed.[3] Work-up then includes imaging of the gland through ultrasound or CT to assess the extent of infection and biopsy as the etiological agents of thyroiditis may cause an indistinguishable clinical presentation.[1,2,4] Ultrasound of infectious thyroiditis typically reveals a unifocal, poorly vascularized hypoechoic nodule with lowest echogenicity in the center and effacement between thyroid and perithyroid tissues.[4,5] CT studies are useful for assessing anatomical tissue involved and abscess extension if present, as well as any underlying structural irregularities like a pyriform sinus fistula that increases risk for bacterial infectious thyroiditis.[3] Ultimately, fine-needle aspiration and/or biopsy with subsequent histological analysis are required to make the diagnosis of fungal thyroiditis as there are shared clinical and laboratory features between bacterial and fungal etiologies.

Treatment of fungal thyroiditis includes patient stabilization and aggressive surgical procedures and/or systemic antifungal therapy, although therapeutic decision is highly dependent on the patient's comorbidities. Surgical techniques utilized are drainage for an abscess, operative debridement for invasive lesions, and partial or total thyroidectomy.[2,3] Pharmacologic treatments may vary depending on the underlying organism, although most drug therapy revolves around the use of Amphotericin B alone or in combinations with fluconazole, itraconazole, or 5-flucytosine.[2,3] Unfortunately, mortality

is high due to most patients with fungal thyroiditis having disseminated infectious disease or immunosuppressed with an underlying hematologic malignancy or from treatment with corticosteroids, chemotherapy, or radiation.[2,3] In the case of our patient, comfort care was provided, and therapeutic treatment withheld due to his deteriorating condition and comorbidities.

Conclusion

Acute anterior neck pain and fever in an immunocompromised patient raises suspicion for infectious thyroiditis. Fungal and bacterial thyroiditis share overlapping symptoms and signs; thus, biopsy is needed for diagnosis and allows for selective antimicrobials to the causative organism(s). Surgical interventions may also be required in select patients for prevention of further infection extension. Clinicians should be especially mindful of fungal thyroiditis in immunosuppressed patients with documented disseminated fungal disease.

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Novel Innovations in Ascites Management

Kyle McKenna Siemers, MS II; Joel Dan Stjernholm, MD; and Christine Pocha, MD, PhD, MPH, FAASLD

Abstract

Ascites in patients with end-stage liver disease and resultant portal hypertension worsens prognosis and accelerates mortality of up to 40% within one year and 50% within two years. In case of refractory ascites, median survival often does not exceed six months due to the development of complications including spontaneous bacterial peritonitis, hyponatremia and renal failure. Additionally, ascites hinders quality of life (QOL) and its management poses a challenge. Sodium restriction and diuresis are the first line treatment which may be limited by renal failure and/or hypotension. Diuretic-resistant ascites may necessitate periodic large volume paracentesis which is invasive and provides only temporary relief. Alternatively, refractory ascites can be curtailed with creation of a trans-jugular intrahepatic portosystemic shunt in very selective patients due to the shunt's propensity to exacerbate hepatic encephalopathy and heart failure. The alfapump system, a novel innovation, is an investigational therapy for ascites management. It is a remotely-rechargeable, battery-operated, subcutaneously implantable device that is designed to continuously divert intraperitoneal ascites into the bladder without external components. This invention is aimed to significantly improve the QOL for patients with ascites.

Ascites – The Conundrum in Patients with Endstage Liver Disease

Ascites is the pathological accumulation of fluid in the peritoneal cavity due to an osmotic pressure imbalance from cirrhosis or portal hypertension. Along with variceal bleeding and hepatic encephalopathy, ascites is a common sign of decompensation of chronic liver disease. Ascites occurs in approximately 10% of cirrhotic patients every year and roughly 60% of cirrhotic patients will develop ascites within ten years of their initial diagnosis of cirrhosis.[1] Once ascites has developed mortality rates rise to up to 40% in one year and 50% within two years. Complications of ascites include spontaneous bacterial peritonitis (SBP), hepatic hydrothorax, and hepatorenal syndrome (HRS) with the latter often leading to death within six months. Overall, ascites is associated with a poor prognosis, poor quality of life (QOL) and its management poses a challenge to the clinician and patient.

In 1996, the International Ascites Club defines uncomplicated ascites as fluid which is not infected and not complicated by HRS.[2] Refractory ascites which occurs in 5-10% of patients is not satisfactorily amenable to medical treatment or recurs early after therapeutic paracentesis. Diuretic-resistant ascites is refractory to dietary sodium restriction and intensive diuretic treatment. Diuretic-intractable ascites is defined by development of diuretic-induced complications hindering effective dosing of diuretic medications.

Pathophysiology

Several hypotheses thought to explain the pathophysiology of ascites and the interplay between portal hypertension, endogenous vasoactive systems, and renal function.[3] The "peripheral arterial vasodilation hypothesis" using splanchnic vasodilation as key component of portal hypertension dominated the past decade. Recently, the role of proinflammatory and pro-oxidative signaling from bacterial translocation gained momentum.[4] Pathogen-associated molecular patterns (PAMPs) from gut bacteria and danger-associated molecular patterns (DAMPs) originating from dying host cells are recognized by toll-like receptors (TLRs) with subsequent production of proinflammatory cytokines.[5] These mechanisms bolster splanchnic vasodilation generated by the activation of the renin-aldosterone-angiotensin system (RAAS) due to perceived hypovolemia.[6]

Complications Related to Ascites

Complications of ascites are linked to increased morbidity and mortality. SBP, often seen in low protein ascites is thought due to reduced quantity of immunoglobulins and complement factors. Patients with SBP can rapidly deteriorate to sepsis with associated circulatory dysfunction further exacerbating arterial hypovolemia. HRS, another feared complication often develops as part of the disarranged circulation during SBP. The negative feedback loop of RAAS activation and hepatic congestion can lead to catastrophic

renal failure. Hepatopulmonary syndrome (HPS) is caused by creation of intrapulmonary vascular dilatations leading to physiologic shunts with subsequent V/Q mismatch. HPS is thought to have a similar pathophysiology as ascites including an increase in production and reduction of hepatic clearance of vasoactive substances.[7] Hepatic hydrothorax occurs in 5-15% of patients with cirrhosis.[8] These patients are at risk of developing a spontaneous bacterial pleural empyema with a similar impact on mortality as SBP. Finally, about 10% of patients develop refractory ascites despite maximized dietary and medical management, requiring additional interventions.[9]

The Old and Current Treatment Options of Ascites

Medical and Supportive Care

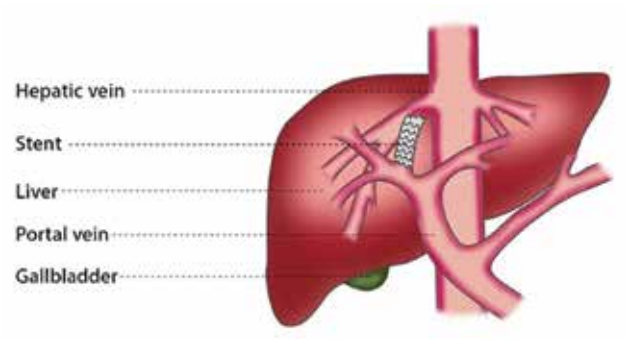
Current recommendations for treating ascites include dietary restriction of sodium, diuretic therapy, and in refractory or severe cases, large volume paracentesis (LVP) with human albumin (HA) administration along with antibiotic prophylaxis for SBP after the first documented episode of SBP.

As secondary hyperaldosteronism is a major factor for renal sodium retention, aldosterone antagonists remain the drug of choice for initial diuresis with added loop diuretics, especially for patients with edema.[10] For patients with significant abdominal distension, LVP can be performed; it is an effective measure to remove fluid although there is a risk of bleeding and iatrogenic infection. Frequent or even weekly paracenteses to handle large, refractory ascites are also contributing to poor quality of life.[11,12] LVPs can lead to post-paracentesis circulatory dysfunction as it reduces the effective circulatory volume and is associated with rapid recurrence of ascites, hyponatremia, renal injury due to HRS, and death.[11,13] To counteract disequilibrium, standard of care includes infusion of 6-8 gram of albumin per liter ascites removed if more than 5 liver removed and as clinically appropriate.[13]

Interventional Therapy – TIPS

Transjugular Intrahepatic Portosystemic Shunt (TIPS) is a way to treat refractory ascites where frequent paracentesis and diuretic therapy are ineffective. TIPS shunts blood past the liver's portal venous system to systemic circulation by connecting the portal vein to the hepatic vein via a stent (Figure 1), thus, lowering the increased hepatic sinusoidal pressure that helps drive ascites formation.[14] Often patients will need to remain on diuretic therapy or need less frequent paracentesis as ascites recurs in up to 30% of TIPS patients.[15,16]

Figure 1. Transjugular intrahepatic portal venous shunt (TIPS).



Post-TIPS encephalopathy is common and reported in 30-50% of patients as ammonia bypass the liver via the shunt. Patients with pre-exiting hepatic encephalopathy (HE) are not suitable candidates for TIPS and others need to be educated about the potential of HE after TIPS.[17] Other contraindications for TIPS placement include advanced liver disease especially with synthetic dysfunction including bilirubin >3mg/dl, MELD score (supplement 1)>15, Child Turcot Pugh score >11 (supplement 2), age > 70, heart failure, and pulmonary hypertension. Controversy over the ability of TIPS to improve survival in cirrhotic patients with refractory ascites remains high. A metanalysis published by Bai et. al. showed that TIPS significantly improved the liver transplant free survival of cirrhotic patients with refractory ascites (HR=0.61, 95% CI: 0.46-0.82, P<0.001), reduced the risk of ascites recurrence OR=0.15, 95% CI: 0.09-0.24, P<0.001 and development of HRS (OR=0.32, 95% CI: 0.12-0.86, P=0.02) but was associated with greater risk of HE (OR=2.18, 95%CI: 1.27-3.76, P=0.005) compared with serial paracentesis.[18] Recent studies of polytetrafluoroethylene (PTFE)-covered stents have shown small improvements.[16,19-20] One study on 70 patients found using covered stents showed significant less TIPS dysfunction (0 versus 82%, p<0.03) in covered stents grafts after 12 months without higher rates of HE.[21]

Decreased liver perfusion can additionally worsen hepatic dysfunction.[22] Careful patient' selection is paramount as the shunt can cause heart failure due to increased blood flow. Finally, extensive cirrhosis may make stent placement in an extremely decompensated patient impracticable.[21]

The use of surgical peritoneovenous shunts (PVS), including Denver or saphenoperitoneal modalities can be considered in the hands of experienced liver surgeons in patients with contraindication for TIPS.[23]

A New Innovation to Treat Ascites

The alfapump system is a novel, investigational device to treat ascites that was approved for commercial use in Europe in 2011. It is an implanted, automated pump that is designed to continuously and independently divert intraperitoneal ascites into the bladder via subcutaneously tunneled catheters (Figures 2-3).[24-26] Four pressure sensors in the device monitor pressure in the abdominal cavity and the bladder in order to instigate a pumping cycle. When the bladder pressure falls below a threshold pressure, a pumping cycle can begin, however, it is halted when the pressure in the abdominal cavity drops where the pump cannot access ascitic fluid. Additionally, pressure sensors within the device validate that the pump is transporting fluid at the programmed rate. The alfapump programmer computer with FlowControl software allows the physician to adjust pumping times, frequency of pumping, and desired daily volume of fluid transported. The device's wireless charging system delivers information about operating time, charging frequency, daily ascites volume, and device dysfunction via mobile phone networks to the manufacturer's secure data specialists who will monitor pump function and send reports to the physician. The pump is continually monitored so the physician can modify treatment and address specific concerns of their patient.

Figure 2. Alfapump system for the automatic and continual removal of ascites.[25]

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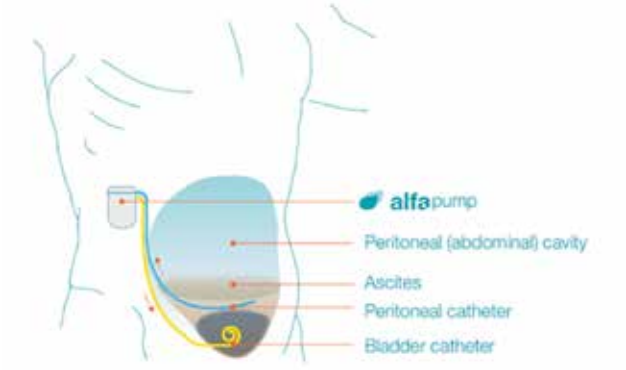
Figure 3. Alfapump in situ.[25]



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The alfapump system is designed for patients with refractory ascites in whom other treatments either medical or interventional (TIPS) are insufficient or contraindicated. The alfapump system provides similar survival data to LVP, however patients experience improved QOL by eradicating the need for frequent LVPs and liver disease-complexing medications.[24] The PIONEER study, a multicenter clinical trial investigating the safety and efficacy of the alfapump system reported a substantially reduced paracentesis frequency from 3.4 to 0.2 per month combined with an acceptable safety profile leading to approval of the device in Europe.[27] Another multicenter European trial which was reported in 2017, concluded that the alfapump system should be considered as a therapeutic option for patients with refractory ascites by reducing the frequency of paracentesis from 2.17 to 0.17 per month. Overall, 66% of patients included in this trial did not require any LVP after implant during the post-implant observation period.[24] If LVP remains necessary, it can be due to complications of the pump itself including clogging, disconnection, technical issues with charging, or volume to pump being programmed too low. Additionally, many patients with refractory ascites deteriorate because of malnutrition due to lack of appetite, reduced food intake, and early satiety due to increased abdominal pressure. Diagnosing and treating malnutrition for these patients is key to avoid progressive frailty. Compared to patients undergoing LVP, patients with the alfapump system showed significant improvement in their nutritional status following implantation.[25] Patients pursuing the alfapump system may require long-term prophylactic antibiotics to prevent SBP, and nutritional support for maintaining a low-sodium diet with sufficient amount of protein and substituting needed deficiencies.

The primary risks of implanting the alfapump system include surgical wound dehiscence and peritoneal cavity infection; therefore broad spectrum intravenous antibiotic prophylaxis are given perioperative. Short-term ascites leakage can occur after implantation, but it typically resolves quickly. Once implanted, the most common cause of pump dysfunction or reason to remove the pump was clogging or blockage of the

catheters by proteinaceous debris, fibrin clots, or aspiration of the omentum. The catheters can also be twisted, displaced, or disconnected after implantation. Re-intervention and replacement of the pump are typically successful in the case of a pump dysfunction. Studies have also reported acute kidney injury following implantation, potentially due to an increase in plasma creatinine or hypoalbuminemia affecting glomerular filtration rate if not the result of a critically ill patient. While patient's kidney function usually improves over time after these events, more data is needed to determine the significance of this adverse event. Contraindications for pump implant are active infection especially SBP or urinary tract infection, reduced life expectancy (typically three to six months), poor functional status, lobulated ascites, and urinary tract obstruction. Importantly, the alphapump system does not interfere with future liver transplant.

Following over a decade of development and the PIONEER multicenter clinical study of its efficacy and safety in 2011, the alfapump system has been widely implemented in the European Union, Switzerland, and Israel as a CE-marked device that costs about €25,000. The CE marking (an acronym for the French "Conformite Europeenne") certifies that a product has met European health, safety, and environmental requirements and ensure consumer safety. In the U.S., the alfapump system has been designated a breakthrough device by the FDA and its outcomes is currently being studied through the POSEIDON study (NCT03973866) in 18 sites across North America.[26] The pump's manufacturer, is also developing a combination therapy of the alfapump system and Direct Sodium Removal (DSR) to address volume overload in patients suffering heart failure.[25]

Overall, the alphapump system may not just be a safe and efficient treatment option for patients with ascites who cannot be sufficiently treated with other medical or interventional modalities but also improve QOL considerably.

Conflict of interest statement – Dr. Pocha has been the principal investigator for the multicenter Poseidon trial at Avera McKennan without direct compensation from the sponsor.

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A Case of Metastatic Uveal Melanoma: From Diagnosis to Survival Four Years Later

Sanyogita Chandra, MS, BA, MS IV; and Heidi McKean, MD

Abstract

Uveal melanoma includes melanoma of the choroid, ciliary body or the iris of the eye and is a rare malignancy that accounts for about 1,500 new cases in the U.S. every year. Of the choroid, ciliary body or the iris, the choroid is most often affected. Local treatment is well-studied; however, this cancer tends to metastasize in nearly 50% of patients, even if the primary melanoma is treated appropriately. There are limited approved treatments for metastatic uveal melanoma and thus, survival rates are low. However, emerging clinical trials demonstrate promising results and play a prominent role in survival of patients with uveal melanoma.

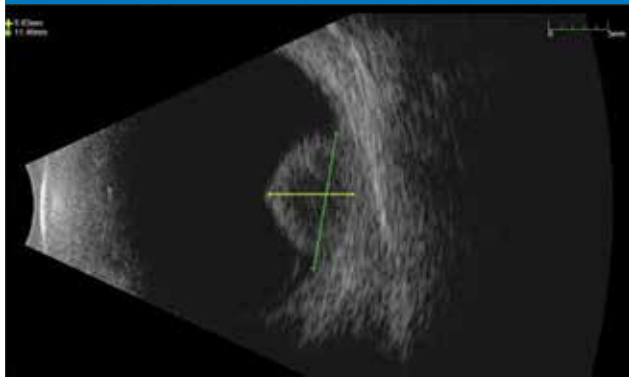
Introduction

Uveal melanoma accounts for only about 5% of melanoma cases and is distinct from cutaneous melanoma, as it presents with different risk factors, anatomic spread, treatment, and responses to systemic therapy.[1] Risk factors include fair skin, light eye color, presence of choroidal nevus, dysplastic nevus syndrome, and dermal melanocytosis. People with BRCA1-associated protein-1 (BAP1) tumor predisposition syndrome are at higher risk for uveal and cutaneous melanomas. It has been theorized that ultraviolet radiation can increase the risk of neoplasia, but this has not been proven.[2] Uveal melanoma has a high tendency to metastasize, especially to the liver (89%), lung (29%), and bone (17%). Unfortunately, 50% of patients with uveal melanoma succumb to metastases within 10 years of diagnosis and median survival after metastasis is between 6-12 months, as treatment is limited after metastases.[3] In fact, one year survival of patients with metastases is reported to be 15%.[4] Gene Expression Profiling of the primary uveal melanoma can be done to assess for the risk of metastatic development. This can be used to stratify the uveal melanoma as Class IA, which means low metastatic risk, Class IB, meaning intermediate metastatic risk, or Class 2, representing high metastatic risk.[5] We present a case of a 50-year-old male with diagnosis of choroidal melanoma with metastasis to the liver four years after initial diagnosis. Four years since classification of metastatic choroidal carcinoma, patient is stable.

Case Report

Eight-and-a-half years ago, a 50-year-old Caucasian male presents to his local ophthalmologist with a two-month history of flashes and blurriness in his left eye as well as a "fan-like motion" in his temporal vision and a "white spot" in the left eye. Fundal photography shows "choroidal melanoma with orange pigment and leaking fluid." Brightness scan ultrasonography shows choroidal melanoma measuring 6.93 mm in width and 11.46 mm in height, low internal reflectivity, and no extraocular extension (Figure 1). Fine needle aspiration of the tumor determines the diagnosis of class 2 choroidal melanoma in the left eye, meaning "his risk of having systemic recurrence for the next 5 years is 72%." Family history of melanoma is not provided for this patient, as he was adopted. At the time of diagnosis, an MRI of the abdomen with and without IV contrast states, "no evidence of metastatic cancer seen in the abdomen, specifically the liver." The patient begins iodine-125 (125I) plaque brachytherapy for seven days. A repeat brightness scan ultrasonography after three months unfortunately displayed growth of choroidal

Figure 1. Brightness scan ultrasonography shows choroidal melanoma measuring 6.93 mm in width (yellow arrow) by 11.46 mm in height (green arrow), low internal reflectivity, and no extraocular extension.



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melanoma to 7.95 mm in width and 13.09 mm in height. Patient continues to have left eye blurriness as well as double vision and a "white spot" in the left eye. Medical oncology recommends patient have MRI of the abdomen every three months for two years and then every six months for an additional three years and then MRI annually after that. CT scan of the chest every six months for two years and then annually is also recommended. Adjuvant therapy with 25 mg sunitinib (Sutent) twice daily for six months is started, as well as photobiomodulation. Patient is also receiving bevacizumab (Avastin) eye injections. Results of MRI of the abdomen with and without IV contrast four months after diagnosis states, "3 mm lesion in hepatic segment 8 at the dome, likely benign and may represent a small cyst or hemangioma."

Three years after Sutent therapy is completed, MRI of the abdomen and pelvis demonstrates a 2.5cm solitary lesion within the right hepatic lobe concerning for metastasis. Biopsy reveals a Melan-A and S100 positive tumor consistent with the diagnosis of metastatic malignant melanoma. Patient undergoes microwave ablation of the lesion five months later. Brightness scan ultrasonography shows choroidal melanoma thickness of 2 mm. Four months later, patient undergoes percutaneous thermal ablation of recurrent tumor of the liver lateral to the previous ablation. Less than a year later, MRI of the abdomen and pelvis demonstrates progression of liver metastases. Patient is restarted on Sutent 25mg daily, but this is soon discontinued due to WBC dropping to 3.1 K/uL (4.5 -11.0 K/uL). Patient undergoes Y-90 radioembolization of liver tumors and begins clinical trial of immunotherapy of ipilimumab and nivolumab therapies. He did develop thyroiditis and vitiligo and begins 75 mcg levothyroxine daily. He completes four cycles of ipilimumab and nivolumab therapies and starts three-year maintenance therapy with nivolumab. Three months later, MRI of the abdomen and pelvis shows stable masses in the liver. CT imaging of the chest shows focal consolidation in right lung base. A month later, repeat CT shows trace right pleural effusion, increased right lower lobe consolidation, as well as a stable right mid lobe nodule. Three months later, MRI of the abdomen and pelvis does not show new focal hepatic lesions. Repeat MRI and CT scans three months and six months later are stable. MRI of the brain with and without contrast states, "no acute or intracranial abnormality." Three months following, MRI of abdomen and pelvis remains stable, and patient has no complaints. CT scan of the chest is remarkable for "right midlung pulmonary nodule measuring 4 x 5 x 4 mm and a change from previous with ground glass in the left anterior midlung that is slightly more prominent. 1 mm subpleural punctate nodule is also new." Although there is a concern for metastasis, given that the patient is asymptomatic and the lung areas are not currently amenable to biopsy, oncology will follow these findings with a CT scan of the chest, abdomen, and pelvis in three months. If nodules have grown, biopsy will be discussed.

Discussion

The uveal tract includes the iris, ciliary body, and choroid. Uveal melanoma presents with painless loss or distortion of vision. Larger tumors present with serous fluid retinal detachment causing photopsia. Ultrasound will showcase low internal reflectivity and intrinsic acoustic quiet zone.[1] Younger patient age at time of diagnosis of uveal melanoma is associated with lower rate of metastases compared to older adults, and the male gender has been found to be associated with significantly higher risk of melanoma-related mortality as compared to the female gender.[3] The relative risk of uveal melanoma assessed in Black, Asian and Pacific Islander, Hispanic, and non-Hispanic white patients was found to be 1:1.2:5:19. Furthermore, the ratio of uveal melanoma in Black compared to white patients is estimated between 1:15 to 1:50. The rarity of uveal melanoma in Black populations is possibly related to protective effects associated with dark skin pigmentation.[6]

Oculodermal melanocytosis is a congenital pigment abnormality with slate-grey pigmentation of the periocular skin, sclera, uveal orbit, meninges, palate, and tympanic membrane and is a risk factor for the development of uveal melanoma. The lifetime risk for white patients with oculodermal melanocytosis to develop uveal melanoma is 1:400. Furthermore, patients with atypical cutaneous nevus are 4.36-10.4 times more likely to develop ocular melanoma than the average population. [6] BAP1 is a nuclear protein that is encoded by the tumor suppressor gene located on chromosome 3p21.2. It is possible that BAP1 protein has a role in regulating cell cycle progression. [2] The BAP1 mutation follows Mendelian genetics, meaning 50% of offspring will inherit the mutation and it predisposes patients to multiple cancers, including uveal and cutaneous melanoma, malignant mesothelioma, basal cell carcinoma, and renal cell carcinoma. A review study showed that patients with uveal melanoma with BAP1 polymorphisms are at a higher risk for larger tumors and higher rates of ciliary body involvement.[6]

Tumor basal diameter and thickness is an important clinical prognostic feature of uveal melanoma. A study finds that the risk of metastasis at five, 10, and 20 years is 6%, 12% and 20% for melanomas <3 mm thickness, 14%, 26%, and 27%

for melanomas between 3.1-8 mm thickness and 35%, 49%, and 69% for larger melanomas. Every millimeter increase in tumor thickness is associated with a 5% increased risk for metastatic spread at 10 years with a hazard ratio of 1.08.[2]

Diagnosis of uveal melanoma includes visual symptoms, tumor thickness >2 mm, presence of subretinal fluid and orange pigment, along with fundal photography showing signs of growth and ocular ultrasound displaying dark, acoustically hollow lesions without a halo.[1] Treatment, if initially limited to the eye, includes diode laser therapy, also known as transpupillary thermotherapy (TTT). Ocular brachytherapy with Iodine-125 is the most common globe-sparking treatment and has shown to be successful in local tumor control.[2] Sunitinib, a multi-targeted tyrosine kinase inhibitor, inhibits driver mutations in the receptor tyrosine kinase c-Kit. Immunohistochemistry analysis shows that >63% of primary uveal melanomas express c-Kit, suggesting it plays a role in tumor growth.[7] One study suggests that sunitinib acts primarily through disease stabilization in metastatic uveal melanoma and thus, could be more beneficial for patients with slow-growing disease.[8]

The liver is the most common organ for metastatic spread and treatment includes surgical resection, hepatic artery embolization, hepatic arterial infusion of chemotherapy, and radiofrequency ablation. Unfortunately, there is no proven standard of care for metastatic disease. Ipilimumab is a human monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and is approved for treatment for metastatic uveal melanoma treatment. Preliminary data states that although the treatment is promising, it has limited clinical activity in both treatment-naïve and pre-treated patients with metastatic uveal melanoma, with median progression-free survival of 2.8 months and median overall survival of 6.8 months.[4] Nivolumab and pembrolizumab are human monoclonal antibodies targeting the programmed cell death 1 (PD-1) receptor and these have also been approved for treatment. Initial assessment of a phase II study shows that use of nivolumab and ipilimumab together had a 18% overall response rate for treatment of metastatic uveal melanoma. The overall survival with nivolumab and ipilimumab treatment is found to be 19.1 months, notably longer than the 6.8-9.6 months reported with a single-agent checkpoint inhibitor, like selumetinib.[7] Furthermore, a meta-analysis of patients in clinical trials with various immunotherapy agents for metastatic uveal melanoma showed median progressive-free survival of 3.3 months with median overall survival of 10.2 months, with a one-year overall survival rate of 43%.[7]

Conclusion

Uveal melanoma is a rare type of melanoma. Risk factors include fair skin and light eye color, as well as conditions including oculodermal melanocytosis and dysplastic nevus. These tumors present with visual symptoms and treatment for localized cancer is well-known. However, most cases of uveal melanoma will metastasize. Treatment for metastatic disease is currently limited. However, clinical trials with nivolumab and ipilimumab have shown promising results.

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Polypharmacy in Older Adults: A Case Study

Christopher Siler, MD, William Fuller, MD, David Whaley, MD; and Jennifer Keating, MD, JD

Abstract

Polypharmacy is defined as concurrent use of multiple drugs for one or more conditions. The occurrence of polypharmacy in vulnerable populations, particularly the elderly, is frequent. Increased incidents of adverse drug reactions and drug-drug interactions plus high costs are not offset by a noticeable improvement in outcome. The practice of polypharmacy persists despite frequent adverse outcomes and reduced effectiveness. We present a case in which an elderly woman presented with falls and delirium. She was taking multiple medications for anxiety and depression in addition to several psychoactive medications for pain, restless leg syndrome, muscle spasms, blood pressure and many nonpsychoactive medications for other conditions. In total, she was taking 24 medications, many of which were likely contributing to her presenting problems.

Introduction

A 2019 World Health Organization (WHO) report estimated that 1 out of every 9 people is considered elderly (age 60 or older), and that by 2050, 1 out of every 5 people will be considered elderly.[1] A study aimed to measure the incidence and prevalence of polypharmacy in 2018 found that approximately 40% of older adults are burdened with polypharmacy.[2] Approximately 21% of intellectually disabled adults are also exposed to polypharmacy.[3] While no standard definition exists, it is the consensus that 5 or more medications per day represent potentially unnecessary overmedication.[4]

Polypharmacy is important to recognize for several reasons. First, "adverse drug reactions (ADRs) occur in up to 35% of outpatients and 44% of hospitalized elderly patients and account for approximately 10% of emergency department (ED) visits. Polypharmacy increases the risk of ADRs from 13% (two medications) to 58% (five medications) to 82% (seven or more medications)."[5] Second, drug-drug interactions (DDI) can range from 2.2%-70%, but typically range from 25%-35% in those exposed. DDI is a preventable consequence that can cause toxicity or reduction in efficacy.[6] Third, polypharmacy can lead to a prescribing cascade, when medication adverse effects are misdiagnosed as symptoms of another disease which can lead to further medications being used to treat adverse effects of the original medications. Fourth, the cost of medications can vary greatly depending on the number and type of medication prescribed. While the average cost of medications for the elderly is around $400-$500 per year, this price can easily reach thousands of dollars. Lastly, polypharmacy can lead to increased pill burden or the number of pills taken per day. Pill burden and high cost can lead to noncompliance. One study showed that the elderly, particularly those from low-income homes, take less medication than prescribed: 22% reported they did not refill a prescription due to cost, 23% reported skipping medications to make the prescription last longer, and 21% reported they spent less on other necessities such as food and heat to be able to afford medications.[7]

With the growth of aging populations, we must learn to recognize polypharmacy and have a willingness to intervene and make changes when appropriate. We present here, a case report of such importance.

Case Presentation

The patient was a 64-year-old female with a PMH of Charcot-Marie-Tooth disorder, T2DM, HTN, HLD and COPD, who presented to the ED after being found unresponsive on the floor of her home. Psychiatry was consulted for guidance with medication reduction of her multiple psychotropic and non-psychotropic medications.

Care Prior to Authors' Involvement

Eight days before her hospitalization, the patient presented with her husband to the ED for epigastric pain starting the day before. A thorough investigation was conducted in the ED and no clear etiology was discovered for her pain. During this time, the ED physician's assessment of the patient noted she "clearly had intellectual disabilities and was a poor historian." ED physician also noted the patient had five folders of bubble packs with various medications being taken incorrectly. At one point, the patient became agitated and combative and received Haldol. ED requested admission to psychiatric

hospital for "agitation, possible psychosis, husband unable to care for patient, poor sleep, poor appetite;" however, she was declined due to concerns of delirium. After the patient presented to a second ED for similar complaints and similar notes of being "more agitated, combative and intermittently confused" with no clear medical etiology, she was cleared for admission. Family, however, decided they no longer wanted admission and with no grounds for civil commitment, she was referred to follow up with her outpatient primary care provider.

Care With Involved Authors

Eight days later, the patient again presented to the ED unresponsive. After being transported to our hospital and thoroughly investigated, the patient was diagnosed with acute encephalopathy secondary to pneumonia and treated with antibiotics. Drug screen was positive for opioids, TCAs, amphetamines, and benzodiazepines. Psychiatry was consulted for concerns of polypharmacy. Her medication list is outlined below. All medications were taken orally unless indicated otherwise.

CNS active medications prescribed for depression, anxiety, and insomnia:

1. Desvenlafaxine 100 mg qd
2. Bupropion SR 150 mg bid
3. Ritalin 20 mg bid
4. Mirtazapine 30 mg qhs
5. Paroxetine 20 mg bid
6. Selegiline 5 mg qd
7. Amitriptyline 40 mg qhs
8. Zolpidem 10 mg qhs

Other CNS active medications:

1. Ropinirole 0.25mg noon and 0.75 mg qhs
2. Gabapentin 600 mg AM, noon and 1200 mg qhs
3. Baclofen 10 mg qhs
4. Oxycodone 10 mg q6h
5. Clonidine 0.1 mg qd and 0.2 mg qhs

Non-CNS active medications:

1. Allopurinol 300 mg qd
2. Famotidine 40 mg qd
3. Ferrous Gluconate 240 mg qd
4. Fluticasone 50mcg 1 spray bid prn
5. Hydrochlorothiazide 25 mg qd
6. Losartan 100 mg qd
7. Meloxicam 7.5 mg bid prn pain
8. Montelukast 5 mg qd
9. Pioglitazone 15 mg/850mg bid
10. Pravastatin 20 mg qd
11. Sucralfate 1 g tid prn GERD

Upon evaluation, patient was pleasant, calm, cooperative, alert, and oriented. She reported a history of "depression and anxiety." She reported stressors related to her current hospital stay and some difficulties with sleep and low energy, but largely denied struggles with mood or anxiety. She reported her primary care physician managed most of her medications and was pleased with the care she had been receiving. She estimated her out-of-pocket cost for her medications to be $12,000 per year. We discussed the risks of being on so many different psychiatric medications and how these should be simplified. While she was hesitant, she eventually agreed.

Her desvenlafaxine, bupropion SR, selegiline and amitriptyline were discontinued. The patient was monitored for any change in vital signs and mental status for withdrawal effects. We also consolidated paroxetine to 40 mg once a day and decreased zolpidem to 5 mg once per night. On follow up the next day, she was tolerating medication changes without difficulty. She was discharged on her new regimen a few days later.

Care After Authors' Involvement

Upon chart review, we discovered that 35 days after discharge, the patient presented to the ED complaining of "not feeling well." Upon further investigation, it was determined the patient had opioid intoxication requiring Narcan and intubation. After the last discharge, she had been restarted on several psychotropic and sedating medications. She also had an entire bubble pack of medication for the previous month essentially untouched, though her husband would report she had been compliant with medications.

Upon pharmacy reconciliation, it was discovered she was now taking the following for depression, anxiety, and insomnia:

1. Methylphenidate 20 mg bid – was listed on med list but patient reported had stopped.
2. Mirtazapine 30 mg qhs
3. Paroxetine 40 mg qd
4. Zolpidem 10 mg qhs - was listed on med list but patient reported had stopped.
5. Eszopiclone 3 mg qhs prn insomnia

Since her last hospitalization, desvenlafaxine, amitriptyline, selegiline, bupropion SR and, per her report, zolpidem and methylphenidate remained stopped. Her UDS was negative for amphetamines, consistent with discontinuation of methylphenidate. Her diagnosis was ruled as acute encephalopathy of unclear etiology with a note to consider polypharmacy vs. less likely septic encephalopathy. The patient was extubated after two days. During this hospitalization, the following changes were made: eszopiclone, zolpidem, oxycodone and methylphenidate were discontinued. Ropinirole was held until follow-up with her primary care physician. Gabapentin was decreased to 300 mg tid. Baclofen was decreased from 10 mg to 5 mg. Amlodipine was increased from 5 mg to 10 mg. Carvedilol 6.25 mg bid was started. Mirtazapine was decreased from 30 mg to 15 mg qhs. Quetiapine 25 mg qhs PRN was started for agitation. Since this second hospitalization, the patient has not presented again to the hospital system.

Discussion

This case exemplifies the complex presentation common with polypharmacy. While pneumonia was likely playing a role, it is possible that several other factors, such as pill burden, DDI/ADRs, and cost were contributing as well.

Pill Burden

In reviewing the patient's medication list from the initial hospitalization, she was on seven medications for symptoms of depression and anxiety (desvenlafaxine, bupropion SR, Ritalin (assuming it was for treatment resistant depression since there was no history of ADD/ADHD or narcolepsy reported), mirtazapine, paroxetine, selegiline, and amitriptyline). She was also on one sedative (zolpidem). The primary rule for reducing pill burden is optimizing dosing before adding an additional medication for the same indication. Only desvenlafaxine was prescribed at maximum dose, while the zolpidem dosage exceeded the FDA approved dose for women. There may have been good reason not to maximize a given antidepressant/anxiolytic medication, but that rationale is unknown without access to outpatient records. It is possible that the patient was unable to tolerate increased doses of her current medications, leading to prescription of additional medications. If that was the case, pharmacogenetic testing could have provided insight on whether the patient's genetics impacted her metabolism of the medications. Abnormal metabolism can increase risk of medication side effects. It can also provide information on whether a patient needs a higher-than-normal dose when compared to someone with normal metabolism. Furthermore, genetic testing can give insight on serotonin transporter gene polymorphism, which can impact medication efficacy.[8] By discharge from her second hospitalization, the psychotropics were reduced from eight to two: mirtazapine and quetiapine PRN. By patient's account, she tolerated the changes well and endorsed continued management of her symptoms (though it is acknowledged that evaluation of benefit was likely premature).

Drug-Drug Interactions and Adverse Drug Reactions

There is a positive correlation between risk of DDI/ADRs and number of medications taken. While several DDI/ADRs were possible based on this patient's medication list, the most serious potential DDI/ADRs related to the medications prescribed for psychiatric conditions.

Serotonin syndrome – Serotonin syndrome results from excessive serotonergic stimulation, classically manifesting as neuromuscular excitation (hyperreflexia, myoclonus, muscle rigidity, tremor), autonomic nervous system excitation (nausea, vomiting, diarrhea, hypertension, tachycardia, diaphoresis, fever >38 degrees C to severe hyperthermia), and altered mental status (anxiety, agitation, confusion, coma).[9] Although rare, serotonin syndrome can result from monotherapy with a serotonergic agent, but that risk increases with the concurrent use of multiple serotonergic agents (i.e., amitriptyline, desvenlafaxine, mirtazapine, paroxetine). When used in conjunction with serotonergic agents, MAOIs like selegiline carry increased risk of serotonin syndrome due to their irreversible inhibition of monoamine oxidase, which leads to increased levels of serotonin as well as dopamine and norepinephrine in neuronal synapses.[10] For this reason, their concurrent use is contraindicated.[11] Clearly administration of multiple SSRI/SNRIs with an MAOI, as was the case here, compounds such risk accordingly.[12]

Hypertensive reactions – Hypertensive crisis (or hypertensive emergency) is defined as elevated blood pressure with evidence of end-organ damage.[13] MAOIs in combination with other medications can lead to a hypertensive crisis by causing a hyperadrenergic state. Concurrent prescription of selegiline and methylphenidate as well as selegiline and bupropion SR are contraindicated due to increased risk of severe hypertensive reactions.[14]

Seizure threshold – Several psychotropic agents, including without limitation antidepressants, antipsychotics, mood stabilizers, stimulants, and MAOIs, lower seizure threshold. Opiates, among other non-CNS active medications (i.e., hypoglycemic agents, antimicrobials, anticancer drugs,

immunosuppressants), carry this same risk. the patient was on several seizure-threshold lowering medications (i.e., amitriptyline, desvenlafaxine, bupropion SR, methylphenidate, paroxetine, oxycodone, pioglitazone), thereby greatly elevating her seizure risk.[15]

Other risks – The patient's medication regimen also placed her at elevated risk for QT prolongation, hallucinations, and medication side effects. Through direct inhibition of the potassium channel, medications like paroxetine and amitriptyline can lengthen ventricular repolarization, leading to torsades de pointes or other potentially lethal arrhythmias.[16] Zolpidem, bupropion SR, and anticholinergic medications can cause hallucinations and, in turn, increase risk for delirium. Through CYP interactions, concurrent use of methylphenidate and certain SSRIs like paroxetine increase their plasma concentrations, generally leading to higher risk of side effects.[17]

The patient's initial hospitalization records indicate she was admitted after being found unresponsive. She was confused with altered mental status. Her blood pressure was 190/72 shortly after admission. Urinalysis showed 3+ blood, 1+ protein. She also had an abnormal EEG, though it did not clearly show evidence of seizure activity. While there was no documented diagnosis of a hypertensive reaction, the elevated blood pressure, hematuria, proteinuria, and abnormal EEG (from which postictal state could not be entirely excluded) certainly raises the question.

On the other hand, while the patient did have AMS, hypertension, and intermittent tachycardia, she was never febrile, nor did she show classic signs of neuromuscular or autonomic nervous system excitation. It is unlikely she had serotonin syndrome, despite being at risk of it. Similarly, EKG did not reveal a prolonged QT. Lastly, it was unclear whether the patient had any symptoms consistent with psychosis. Documentation from the second ED visit noted that the patient had "possible psychosis," but it was unclear whether that was based on provider evaluation or family reports. There was no documented reports of hallucinations or response to internal stimuli while hospitalized.

Cost

Despite having private insurance, the patient reported spending more than $1,000 per month for all her medications. Assuming for purposes of demonstration that she did not have insurance, her retail cost for the original eight psychiatric medications would have decreased from $253-$1,203/month to $18-$182/month for the mirtazapine and quetiapine.[18] Such a drastic reduction in cost makes medication compliance more likely as the patient would not have to forego other necessities in order to afford them. As with pill burden, DDI and adverse reactions, the primary rule for reducing medication cost is to maximize the dosing of a medication for a condition before adding an additional medication for the same indication. Utilizing generics before brand name medications can be beneficial for cost reduction as well.

Conclusion

Polypharmacy can carry dire consequences for patients not only in terms of DDIs and ADRs, but also in terms of pill burden and cost, among others. From a psychiatric standpoint, the patient was on an unusual medication regimen that was fraught with risk for difficulties, both health-wise and financially. The patient found herself hospitalized at least twice, probably partly due to the number of medications she was on and the interactions among them. Judicious use of medications can be helped by reviewing medication lists regularly, maximizing medications before adding additional ones, using medications indicated for the multiple psychiatric symptoms, computer cross-referencing DDIs, using pharmacogenetic testing when indicated, or simply discontinuing medications that are of limited benefit. To improve outcomes, this case emphasizes the importance of close communication and follow through among all physicians involved in a patient's care as well as with family members. While it is easy to declare best practices, oftentimes the realities of clinical practice can thwart the best of intentions.

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Disseminated Mucormycosis from Marijuana Use in a Renal Transplant Patient

Kayla Hoerschgen, MD; and Ashwyna Sunassee, MD

Abstract

Mucormycosis is a serious fungal infection that typically affects immunocompromised patients. We present a case of disseminated mucormycosis infection in a 34-year-old male with a history of marijuana use and focal segmental glomerulosclerosis who underwent living unrelated kidney transplant. After his transplant, he developed recurrent focal segmental glomerulosclerosis. Two months later, he developed pleuritic chest pain and imaging revealed a ground glass opacity with a surrounding dense consolidation within the right upper lobe, concerning for an angioinvasive fungal infection. During the hospitalization, his creatinine increased, and a biopsy of the allograft kidney demonstrated acute tubulointerstitial nephritis, acute vasculitis, and glomerular intracapillary fibrin thrombi with angioinvasive Mucorales fungal infection. The patient subsequently underwent transplant nephrectomy. Grossly, the allograft was pale white to dusky tan-red with poorly delineated cortical medullary junctions. Microscopic examination revealed necrotic tubules with a dense neutrophilic infiltrate, multinucleated giant cells, and ribbon-like, aseptate hyphae. A Gomori's methenamine silver stain highlighted the fungal elements, which were morphologically consistent with Mucorales. Review of the literature revealed that the incidence of mucormycosis within the first year is low at approximately 0.07% for renal transplant patients with an estimated overall mortality of 40-50%. Additionally, few case reports have been published demonstrating marijuana use as a cause of pulmonary mucormycosis or even disseminated disease. The purpose of our case report is to add knowledge to the presenting symptoms and investigate the association of marijuana use with pulmonary and disseminated mucormycosis.

Introduction

Fungal infections remain a high threat for solid organ transplant patients. The infections can be due to endogenous organisms reactivating during immunosuppression, donor-acquired organisms, or from the environment.[1] Mucorales fungi are the second most common pathogens in patients with solid organ transplant, hematologic malignancies, and hematopoietic stem cell transplant, second only to *Aspergillus*.[2] Mucorales molds cause aggressive, life-threatening disease. These ubiquitous spore forming molds grow best in warm, moist environments with severe infections occurring due to inhalation of spores that affect the immunocompromised.[3] The common presentations include rhino-cerebral, pulmonary, cutaneous, gastrointestinal, and renal. The incidence of mucormycosis occurring in a renal allograft is low.[4] Additionally, only a small number of case reports demonstrate patients acquiring invasive pulmonary fungal infections from marijuana smoking, but none have demonstrated Mucorales in a solid organ transplant patient. Here we present a case of a 34-year-old male with a history of marijuana use and focal segmental glomerulosclerosis who underwent living, unrelated kidney transplant and developed disseminated mucormycosis involving his renal allograft. This case adds knowledge to the presenting symptoms, demonstrates a rare cause of mucormycosis, and highlights the importance of educating patients with immunocompromising conditions to the risks associated with marijuana use.

Case Presentation

A 34-year-old male with a history of marijuana use, treated hepatitis C with sustained virologic response (2018), and end-stage renal disease secondary to focal segmental glomerulosclerosis diagnosed in 2008 underwent a kidney transplant from a living, unrelated donor. A few days after the transplant he underwent a biopsy of the allograft and was found to have severe podocyte injury consistent with recurrent primary focal segmental glomerulosclerosis. He received treatment with plasmapheresis, thymoglobulin, and rituximab and was discharged. A month later he presented to clinic for routine transplant follow-up with subsequent hospital admission for a fever, severe dysphagia/odynophagia, abdominal pain, and malnourishment. Initial infectious workup with urinalysis and chest x-ray were

unremarkable. An esophagogastroduodenoscopy revealed large serpiginous ulcers in the esophagus and a stomach ulcer, which were biopsy negative for organisms. Further infectious disease workup for fungal and viral organisms remained unremarkable. A few days after admission, he developed pleuritic chest pain and a high-resolution CT of his chest revealed a 14 mm central ground glass opacity surrounded by a denser consolidation within the right upper lobe (reverse halo sign) (Figure 1) and diffuse centrilobular nodules concerning for an angioinvasive fungal infection. Antifungal treatment was initiated with voriconazole, however, repeat fungal panels remained negative and the antifungal was discontinued after a couple of days. During this same time, his creatinine steadily increased, and a biopsy of the renal allograft revealed acute tubulointerstitial nephritis, acute vasculitis, and glomerular intracapillary fibrin thrombi with angioinvasive Mucorales fungal organisms. A CT scan of his sinuses was unremarkable, and the source of infection was favored to be pulmonary origin secondary to marijuana smoking with dissemination to the renal allograft. The patient was immediately started on posaconazole and liposomal amphotericin B. His immunosuppression was decreased, and he underwent renal allograft nephrectomy.

Grossly, the allograft was pale white to dusky tan-red with poorly delineated cortical medullary junctions. Microscopic examination revealed necrotic tubules with a dense neutrophilic infiltrate, multinucleated giant cells (Figures 2 and 3), and ribbon-like, aseptate hyphae (Figure 4). A Gomori's methenamine silver stain highlighted the fungal

Figure 1. Axial CT of the lungs showing an opacity surrounded by a denser consolidation within the right upper lobe.

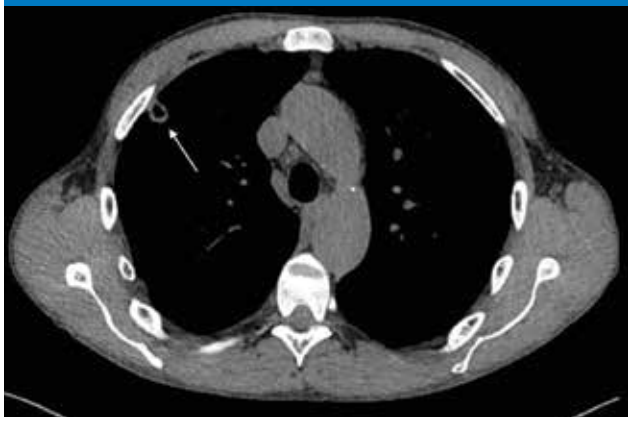


Figure 2. Renal parenchyma with a dense neutrophilic infiltrate and multinucleated giant cells. Hematoxylin and eosin stain, 10X magnification.

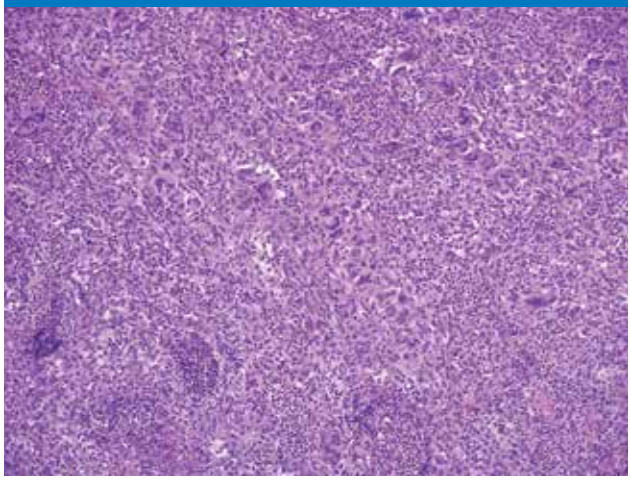


Figure 3. Necrotic tubules (arrows) with a dense neutrophilic infiltrate (right). Hematoxylin and eosin stain, 10X magnification.

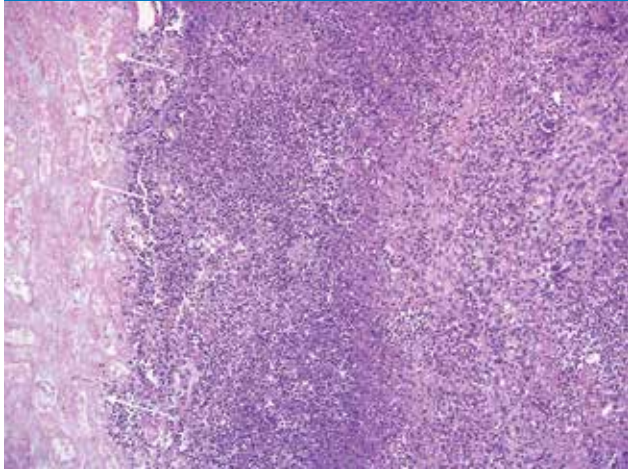


Figure 4. Neutrophilic infiltrate surrounding ribbon- like, aseptate hyphae. Hematoxylin and eosin stain, 40X magnification.

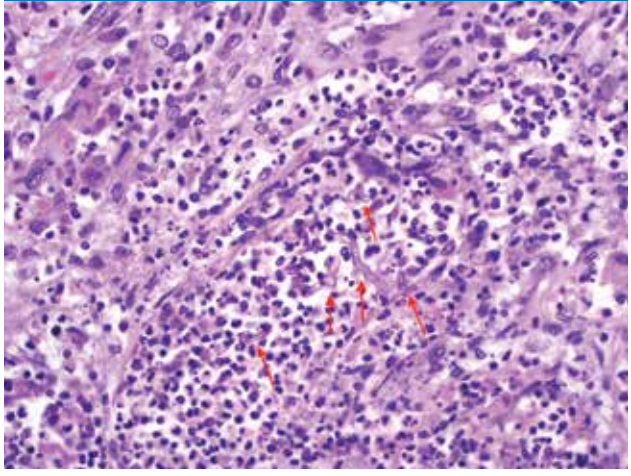
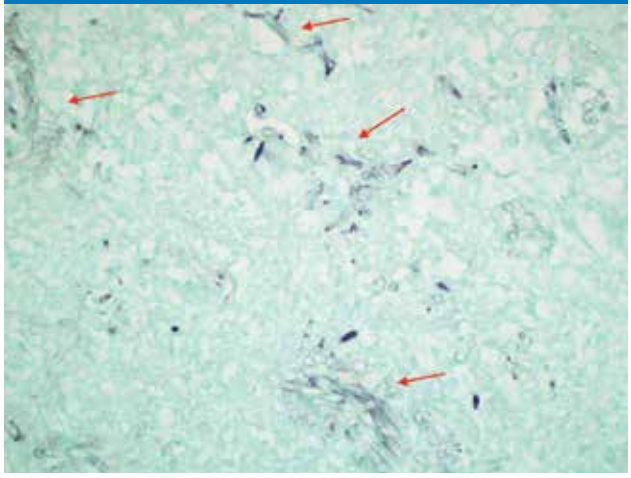


Figure 5. Fungal hyphae within renal parenchyma. Gomori's methanamine silver (GMS) stain, 40X magnification.



elements (Figure 5), which were morphologically consistent with Mucorales.

Discussion

Mucormycosis refers to a severe, life-threatening disease with several disease manifestations caused by a group of angioinvasive molds called mucormycetes, which belong to the order of Mucorales. The most common types that cause infection include *Rhizopus, Mucor, Rhizomucor, Syncephalastrum, Cunninghamella, Apophysomyces, Lichtheimia, and Saksenaea*.[3,5] Mucormycetes produce spores and live throughout the environment, especially in the soil and decaying vegetation. Infection typically occurs after direct cutaneous contact and/or inhalation of the spores in immunocompromised individuals.[3] Common sites of infection include rhino-cerebral, pulmonary, cutaneous, gastrointestinal, central nervous system, or disseminated (infection of two non-contiguous sites) manifesting as hemorrhagic necrosis, vascular thromboses, and tissue infarction.[3,4,6] This opportunistic infection is commonly reported in middle aged men with diabetes mellitus; however, patients with other immunosuppressive conditions like HIV, solid organ transplant, malignancy (including hematologic), hematopoietic stem cell transplant, and with prolonged use of steroids are at increased risk.[2,4] Additional risk factors are previous exposures to voriconazole and caspofungin.[2,3,6]

Mucorales infection in renal transplant patients has been estimated at 0.2% to 1.2%, however, these infections have increased over the last decade.[7] Solid organ transplant recipients are at greatest risk of fungal infections during the initial 6-12 months, however, mucormycosis develops within three to six months post-transplant.[1,3] These patients demonstrate pulmonary, gastrointestinal, and disseminated forms of the disease.[2] The mortality rate amongst solid organ transplant recipients with mucormycosis is not well defined, but overall mortality has been estimated at 40-50% and up to 71%.[2,7] While the mortality rate of the disseminated form is higher at 76% in one study and even up to 96% in another.[4,7]

In addition to the growing amount of mucormycosis infections, marijuana use has also increased within the past decade with many states legalizing its use medicinally. According to the 2019 National Survey on Drug Use and Health 17.5% of respondents reported using marijuana in 2019, as opposed to 11% in 2002.[8] Despite its increased use, appropriate universal standards to regulate contaminants have not been created. One study reported up to 20 different fungal genera to include Mucor, and gram-negative bacteria contaminating marijuana being sold for medicinal use.[9] Cannabis plants, whether grown indoors or out, can contain fungi and bacteria from the growing conditions, all the way to the subsequent handling and processing.[5] While most of the organisms do not pose a significant risk to most users, immunocompromised patients are at an increased risk. Several case reports have demonstrated invasive pulmonary fungal infections, primarily *Aspergillus,* associated with marijuana smoking in patients with hematologic malignancies.[5.] With no set standards for acceptable contaminants, it is imperative immunocompromised patients be informed/counseled on the potentially dangerous consequences of smoking marijuana.

Diagnosing mucormycosis is challenging because symptoms are non-specific and are dependent on the organ system affected. Rhino-cerebral and pulmonary infections are better characterized because they are more common.[4] Those with rhino-cerebral infections present with facial or orbital pain and swelling, proptosis, visual loss, and with brain involvement, headaches, altered mentation, seizures and strokes. Whereas pulmonary infections present with fever, pleuritic chest pain, or features of pneumonia.[6] Signs suggestive of graft kidney mucormycosis can include fever, abdominal pain, oliguria, and graft dysfunction.[4] Diagnosis is confirmed by a combination of radiologic, histopathologic, and microbiological studies.[6] Plain or contrast enhanced CT images of the chest commonly show consolidation or mass-like lesions, nodules, or cavities, while sinus involvement is demonstrated by opacification of the maxillary sinus.[6] Majority of cases are diagnosed with histology and microbiology.[2,4,6] Histologically, the fungi have broad, aseptate, or pauci-septate hyphae with wide angle branching

with tissue invasion.[2,6] Microbiologic culture and molecular techniques may aid in genera/species identification.[2]

Once a diagnosis is made, treatment should be started immediately. Mortality rates are lower in patients treated with surgical debridement and antifungal therapy, than either alone.[4,6] The first line agent is amphotericin B, lipid complex or liposomal form. Posaconazole also has activity against Mucorales and may be employed if a patient is intolerant to Amphotericin B, in combination with amphotericin B if refractory infection, or as step down treatment after successful response to amphotericin B.[3,6] Studies are inconclusive on the benefit of amphotericin B and posaconazole combination therapy; however, the decision was made to start the patient on both because of the high mortality rate associated with the infection.[3] Additionally, immunosuppression should generally be reduced and surgical debridement of affected areas should be performed.[3,5,6]

Mucormycosis infections are rare among renal transplant patients but have a high mortality rate. Timely diagnosis and combined treatment with surgical debridement and antifungals has been shown to lower mortality. Our case highlights a rare cause of disseminated mucormycosis and emphasizes the importance of counseling immunocompromised patients on the use of marijuana.

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Preventing Unintended Pregnancies: A Review of Long-Acting Reversible Contraception

Megan Torve, MS IV; and Keith Hansen, MD

Abstract

With increasing uncertainty surrounding female reproductive rights, patient education about contraceptive options is of paramount importance. Although traditional oral contraceptive pills (OCP) are often used to prevent pregnancy, they require precise, daily effort and have continual monetary maintenance costs for patients. Long-acting reversible contraceptives (LARCs) – intrauterine devices and the contraceptive implant – are effective and reliable alternatives to OCPs that are gaining popularity in the U.S. These contraceptive options do not require continual patient maintenance and are overall cost-effective. Physicians should be well versed in what contraceptive options are available for their patients and comfortable providing education and recommendations. This analysis will cover what LARCs are on the U.S. market, risks and benefits of each, as well as the CDC's medical eligibility criteria.

Background

The oral contraceptive pill (OCP) is a common form of contraception in the U.S., though neither the most effective nor the easiest to use.[1] Consistent, correct use of OCPs does achieve a 99% success rate in preventing pregnancy, but typical use – human error leading to missed or incorrectly timed doses – decreases their efficacy to 91%.[2] OCPs must be taken at the same time every day, interact with many medications, including antibiotics, and missing even one dose can lead to unintended pregnancy. While the rate of unintended pregnancies has decreased in the U.S., from 51% of pregnancies in 2008 to 45% in 2011,[3] typical use of contraceptives accounts for 41% of unplanned pregnancies while actual contraceptive failure accounts for only 5%.[4, 5]

Long-acting reversible contraceptives (LARC) are safe and effective contraception methods that should be routinely offered to patients. LARCs provide consistent, efficacious contraception that by design removes the potential for human error. Increased use of LARCs decreases unintended pregnancies, high-risk births, and abortion rates.[6,7] Though initial cost is higher, the cost equalizes before three years of use, making LARCs cost-effective alternatives to OCPs.[8] Return of fertility is immediate for women who desire pregnancy and removal can be done in office by a trained physician.[9]

What is Available

There are currently six available LARCs – four levonorgestrel-releasing intrauterine devices (LNG-IUDs), the copper containing IUD, and the etonogestrel-releasing contraceptive implant. While there is slight variance in the efficacy of each LARC, typical use pregnancy rates are up to 20 times lower than oral contraceptives.[10]

Levonorgestrel-Releasing IUDs

LNG-IUDs function primarily by thickening the cervical mucus and impairing sperm motility so that fertilization cannot occur.[11] Because of this mechanism, LNG-IUDs are not abortifacients and are not approved for use as emergency contraception. LNG-IUDs are commonly associated with three to six months of irregular bleeding and spotting that typically settles into shorter, lighter periods or no periods at all.[12-15] Other hormonally mediated side effects include

Table 1. Comparison of typical use and perfect use accidental pregnancy rates.

	Percentage of pregnancy during the first year of use	
Method	Perfect use*	Typical use**
Combined pill and progestin-only pill	0.3	9
Intrauterine device		
Cu-IUD	0.6	0.8
LNG-IUD	0.2	0.2
Implant	0.05	0.05

*Among typical couples who initiate use of a method (not necessarily for the first time), the percentage reflects women who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
**Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (consistently and correctly), the percentage reflects women who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
Adapted from: Trussell J. Contraceptive failure in the United States. Contraception. 2011 May;83(5):397-404.

nausea, breast tenderness, mood changes, ovarian cyst formation, and rarely, acne.[9]

There are two 52 mg levonorgestrel IUDs that release 20 micrograms of levonorgestrel a day, the Mirena IUS (Bayer, Whippany New Jersey), which has been approved for use as birth control for seven years; and the Liletta (AbbVie Inc., North Chicago, Illinois) which has been approved for six years of use.[12,13] The Kyleena (Bayer, Whippany New Jersey), contains 19.5 mg of levonorgestrel, releases 17.5 micrograms a day, and can be used for five years.[14] The shortest use LNG-IUD, approved for three years, is the Skyla (Bayer, Whippany New Jersey), with 13.5 mg of levonorgestrel, 14 micrograms released a day. [15]

LNG-IUDs can be inserted at any point in a woman's menstrual cycle. If insertion occurs within the first seven days of the cycle (since the first day of bleeding) no backup contraception is necessary. If insertion occurs later, abstinence or alternative contraception – condoms, diaphragms, spermicides – are required for seven days post-insertion to ensure prevention of pregnancy. In the amenorrheic patient, caution should be exercised, and abstinence or alternative contraception should be recommended for seven days post-insertion.[16]

Copper-containing IUD

The Paragard (CooperSurgical, Trumbull, Connecticut), is the only copper-containing IUD on the market and is approved for 10 years of use.[17] It exerts its effect via local cytotoxic inflammation that prevents both sperm motility and viability.[18] This inflammatory effect, mediated chiefly by prostaglandins, is also associated with increased menstrual bleeding that is cited as a major cause of copper containing IUD removal.[19-21] NSAIDs should be considered both for acute increased bleeding and prophylactically in patients who desire a Paragard IUD.[19]

The Cu-containing IUD is effective when inserted at any point of a woman's menstrual cycle. Use of back-up contraception is not necessary.[16]

IUD Risks

Risks of IUDs fall into two major categories – insertion and post-insertion. Though rare, the most concerning risk of inserting an IUD that should be discussed with patients is uterine perforation. Rate of insertional uterine perforation is similar with all types of IUDs and is reported as 1 in 1,000 insertions with use of proper technique. Gradual erosion of the endometrium causing later perforation is also possible.[22]

Insertional complications, including difficulty with cervical dilation (or inability to dilate) and vasovagal symptoms, are more common in nulliparous women and older women. These events can be observed in any population and all patients should be informed of these risks.

Post-insertional complications include displacement causing discomfort and accidental removal of the IUD. Expulsion occurs in 2-10% of patients within the first year after insertion, typically within the first three months.[23,24] Expulsion is more common in multiparous women and is seen at increased rates when inserted immediately postpartum. Patients are routinely instructed to regularly check strings to ensure that their IUD is still in place.[23] If the strings are ever absent, a pregnancy test should be performed. If strings are absent and a pregnancy test is negative, an ultrasound should be performed to ensure intrauterine placement of the device. If the device is in place, it can be left in the uterus for the remainder of its therapeutic duration. If the device cannot be visualized by ultrasound, a plain-film radiograph is indicated to ensure that the device has not perforated into the peritoneal cavity.[25]

In the rare event that a patient becomes pregnant with an IUD in place, she should be advised to have the IUD removed due to risk of spontaneous abortion, septic abortion, chorioamnionitis, and preterm delivery.[26] Removal of the IUD reduces these risks, though it does not eliminate them.

Contraceptive Implant

The contraceptive implant is an etonogestrel releasing LARC that is placed subdermally, typically in the upper portion of the non-dominant arm. The implant is designed for controlled release of its 68 mg of etonogestrel over a three-year period.[27] The etonogestrel suppresses the mid-cycle LH surge, thereby suppressing ovulation while also thickening cervical mucus.[28] Typical-use pregnancy rate is 0.05%, making it the most effective contraceptive on the market.[29]

Side effects of systemic etonogestrel include unpredictable changes in menstrual bleeding, headaches, breast pain, worsening of acne, and gastrointestinal symptoms. Weight gain is noted in 12% of implant users and is a common cause of discontinuation.[9]

The contraceptive implant can be inserted at any time during a woman's menstrual cycle. If insertion occurs within the first five days of the cycle (since the first day of bleeding) use of backup contraception is not necessary. If insertion occurs greater than five days after the beginning of the

cycle, abstinence or additional contraception is required for seven days to prevent pregnancy. Similarly, if the patient is amenorrheic, abstinence or additional contraception should be recommended for seven days.[30]

Special considerations exist if a patient is switching from an IUD to the contraceptive implant. If the patient has had sexual intercourse in the past seven days and it has been greater than five days since the beginning of her current menstrual cycle, it is possible that there may still be sperm in the genital tract and fertilization could occur if she ovulated. In these cases, the patient should be advised to either abstain from sexual intercourse or use additional contraception for seven days before removal of the IUD and insertion of the contraceptive implant. Alternatively, the contraceptive implant can be inserted, and the patient advised to return in seven days for removal of the IUD.[30]

CDC Medical Eligibility Criteria

The CDC's medical eligibility criteria outline clinical practice guidelines for contraceptive use, including LARCS, in patients with additional medical conditions. Risk factors are divided into four classification categories: 1 = no restriction to the method of contraception, 2 = advantages typically outweigh the risks of the contraceptive method 3 = risks typically outweigh the advantages of the contraceptive method, and 4 = the contraceptive method confers unacceptable health risks. While choice of LARC is equivocal for many medical confounders, there are certain conditions where one may be preferable to another.

The following medical conditions are classified in category 1 for the Cu-IUD and category 2 for LNG-IUDs and the contraceptive implant. Any form of LARC is generally considered advantageous in these conditions, though the Cu-IUD may be better tolerated

- Breastfeeding
- Multiple atherosclerotic cardiovascular disease risk factors, history of ischemic heart disease, history of stroke
- SLE with positive antiphospholipid antibodies on immunosuppressive therapy
- Cervical intraepithelial neoplasia
- Undiagnosed breast mass
- Cholecystitis – either current or previous, symptomatic, or asymptomatic
- Focal nodular hyperplasia
- History of DVT/PE, prolonged immobilization, known thrombogenic mutations[31]

Conditions in which the Cu-IUD is clearly safer include hormonally mediated conditions such as active breast cancer (Cu-IUD category 1, LNG-IUD/implant category 4), severe cirrhosis (Cu-IUD category 1, LNG-IUD/implant category 3), hepatocellular adenomas and malignant hepatomas (Cu-IUD category 1, LNG-IUD/implant category 3).[31]

In patients with bleeding disorders, the Cu-IUD may worsen their condition. Patients with irregular, heavy menstrual bleeding, endometriosis, or severe dysmenorrhea may tolerate the LNG-IUD or contraceptive implant better than the Cu-IUD, though these conditions are considered Cu-IUD category 2. Additionally, patients on HIV medication regimens are placed in LNG-IUD category 1 and Cu-IUD category 2.[31]

Pelvic conditions that are in category 4 are considered relative contraindications to the insertion of either the Cu-IUD or an LNG-IUD. In these cases, the contraceptive implant is a suitable alternative. These conditions include:

- Anatomic abnormalities that distort the uterine cavity
- Current or recent postpartum sepsis, recent chorioamnionitis, current endometritis, post-septic abortion
- Confirmed gestational trophoblastic disease with elevated ß-HCG and evidence of malignant or intrauterine disease
- Untreated cervical cancer or endometrial cancer
- Current PID, cervicitis, chlamydial infection, or gonorrheal infection, pelvic Tb [31]

Age and nulliparity are by no means contraindications to intrauterine contraceptive devices, but young patients who have not had previous vaginal deliveries may better tolerate insertion of the contraceptive implant than insertion of an IUD.[31]

Theoretical risks do exist for drug interactions between the contraceptive implant and certain medications such as phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, rifampin, St. John's wort and some HIV medications – primarily regimens including ritonavir, fosamprenavir, and nelfinavir. Patients taking any of these medications would benefit from use a contraceptive implant (category 2) with proper education about the potential interaction or from insertion of an IUD.[31]

No form of birth control should be initiated if a patient is pregnant. If a patient has unexplained abnormal vaginal

bleeding, it should be thoroughly evaluated before any birth control is started.[31]

For a more complete list of recommendations for patients with specific conditions, the Centers for Disease Control and Prevention *Medical Eligibility Criteria for Contraceptive Use, 2016* is readily available from the CDC Reproductive Health website.[30] Additionally, the free CDC Contraception app is a convenient way to access the medical eligibility criteria.[32] The app is available for Apple and Google devices.

Conclusion

Long-acting reversible contraceptives are exceptional options for patients who want reliable, low maintenance pregnancy prevention. They are more effective with typical use than OCPs, are comparatively cost effective, and have a favorable side effect profile. For conditions that exclude one form of LARC, others are available that provide equitable protection. Physician education and preparedness to discuss these options with patients is foundational to further prevention of unintended pregnancies and unfavorable outcomes for patients.

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Home-based services encompass a wide range of offerings from medical care and rehabilitation therapies to assistance with everyday household activities and shopping. These services are provided to people of all ages in their homes.

Inpatient and outpatient rehab therapy
Our rehabilitation services are for people of all ages who would benefit from additional therapy to enhance recovery after a hospitalization, illness or injury.

Our Medicare-certified inpatient and outpatient rehab programs feature therapy gyms and include physical, occupational and speech therapy. We offer tailored services to meet the patient's needs.

Long-term care
We offer around-the-clock care that supports our residents and meets their needs. We help anyone in need of long-term care, including rehabilitation therapy or skilled nursing care.

Our long-term care communities offer:

- On-site licensed therapists
- Social and spiritual activities
- Around-the-clock, personalized care
- Nutritious meals
- Barbershops and salons
- Care planning with residents' family

All in one place
Our goal is to provide the care and services our residents need to live their best life. We strive to deliver the highest quality of care to each resident and are dedicated to enhancing their lives by giving attention to the finer details of everyday life so they get the time and opportunities to focus on what matters most to them.

For more information on the services we offer, and to learn how to refer a patient, visit our referral partners page at good-sam.com.

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South Dakota Physician Well-Being Program Starts Peer-Support Groups

Social Gatherings Combat Burnout and Improve Resiliency

Beth Jensen, DO

Physicians are the backbone of a high-performing health care system. But recent surveys show that health systems across the world are facing a crisis of potentially declining quality of care[1] as well as physically and mentally overburdened physicians. According to the 2022 Well-Being Index[2] and other recent analyses, physician assessments revealed the following:

- 54% of physicians reported burnout
- Over half of physicians reported emotional problems
- Four common specialties reported the highest percentages of distress: neurology, emergency medicine, radiology and pediatrics
- Suicide rates among U.S. physicians is highest among all professions[3]

The crisis is even more concerning as we recognize how few physicians seek out mental health services to address needs for themselves. There are a variety of factors that can contribute to why physicians may be less likely to seek out mental health care services than the general population. Some potential reasons include perceptions of stigma, lack of confidentiality, time constraints and lack of familiarity to recognize the signs and symptoms of mental health conditions in themselves and others.

The South Dakota Physician Well-Being Program (SDPWBP) is a response to addressing this critical need to recognize and improve mental health care access to physicians in need. South Dakota physicians seeking support for their health and well-being now have a confidential and professional resource. Contracted through Midwest Health Management Services, the SDPWBP is a responsive, high-quality program for physicians and residents that offers confidential, individualized support services and resources. The SDSMA, with funding assistance from Avera Health, Monument Health and Sanford Health, has developed this program as a resource for all South Dakota physicians.

We seek evidence-based approaches to prevent and treat burnout signs and symptoms among South Dakota physicians. One exciting and important addition to our program includes peer-to-peer support groups. A growing amount of literature reveals that peer support groups are among the most effective ways to combat burn-out and improve resilience. Their purpose is to provide a safe space for individuals struggling with similar issues to come together and share their experiences, vent emotions, ask for advice, and receive support from each other. Peer support groups differ from individual therapy in a few ways, most notably that participation in peer support groups is voluntary and does not need the presence of a healthcare professional.

The importance of peer support groups, when it comes to the medical and mental health field, is often overlooked. Peer support groups have been found to have profound impacts on the mental and physical health of individuals seeking help. For physicians, the presence of other individuals who have gone through similar experiences can be empowering and validating. Evidence suggests that the peer relationships created in these groups often result in lasting emotional, physical, and psychological growth for each group member. Members often develop a sense of trust and camaraderie when sharing their experiences, which can lead to increased self-efficacy, self-esteem, and overall well-being.

The South Dakota Physician Moms Group – Physician moms have unique work/life balance concerns. This group provides a safe and supportive environment to hear other women talk about how to juggle it all. The South Dakota Physician Moms Group meets via Zoom (so no need for additional childcare!) the first Tuesday of every month from 7-8 pm CT. Contact us if you are interested to learn more details. Dr. Beth Jensen (elizabethj@mwhms.com) facilitates the South Dakota Physician Moms Group.

The South Dakota Retired Physicians Group meet monthly at The All Day Cafe in Sioux Falls. They decide at the end of each meeting when the next month's meeting will occur. This warm, wise and talkative group gathers for coffee and reminisces about the dramatic lifestyle differences through which they've lived. Drs. Dan Heinemann (djheineman@aol.com) and Tad

Jacobs (doctalkconsulting@gmail.com) host the monthly Retired Physician Group in Sioux Falls. Meeting times vary therefore email either host to find out when they're meeting next.

Figure 1. Attendees of the first meeting of the Retired Physicians Group on Feb. 9. Left to right: Drs. Ray "Gene" Nemer, Jim Oakland, Bob Santella, Ken Augspurger, Dean Madison, Earl Kemp, Tad Jacobs, Dan Heinemann.

Overall, it is clear that peer support groups have immense potential to positively impact the mental and physical health of physicians. From providing social support and a better quality of life to helping reduce symptoms associated with mental illnesses and substance use disorders, peer support groups can play a crucial role in the overall health and wellbeing of our medical providers.

Ensuring that all physicians have access to, and take advantage of, mental health services is critical. Physicians are the backbone of a high-performing health care system. We must speak more openly about our common struggles and seek help if we need it. If you are a physician mom or retired physician, please join one of our peer-to-peer groups! As you can imagine, participating is one of the most enjoyable ways to improve well-being.

If you are struggling with symptoms of mental illness, such as depression, partner relationships or substance abuse concerns, you are not alone. Recovery is a realistic expectation if we ask for and accept help. The SDPWBP emphasizes confidentiality, respects your time and applies the gold standard of mental health treatments for all participants. We are eager to hear from you.

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1. Weigl M. Physician burnout undermines safe healthcare. BMJ. 2022 Sep 14;378:o2157.
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3. Irigoyen-Otiñano M, Castro-Herranz S, Romero-Agüit S, Mingote-Adán JC, Garrote-Díaz JM, Matas-Aguilera V, López-Ordoño GJ, et al. Suicide among physicians: major risk for women physicians. Psychiatry Res. 2022 Apr;310:114441.

About the Author:

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Member News

Visit www.sdsma.org for the latest news and information.

2023 SDSMA Annual Leadership Conference is June 2

The 2023 SDSMA Annual Leadership Conference is Friday, June 2 at the Hilton Garden Inn Downtown Sioux Falls.

Events and Activities

- Update from the University of South Dakota Sanford School of Medicine
- Update from the American Medical Association
- Panel discussion
- Membership open forum
- SDSMA PAC lunch
- Medical student poster session
- Policy Council meeting
- Membership mixer
- Awards banquet & scholarship recognition

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

The conference is a benefit of your membership and there is no conference registration fee for members. The full schedule and registration will soon be available at sdsma.org.

Ticket purchase required for some events and meals.

South Dakota Coalition For Excellence in Patient Care Update

Optometry scope of practice expansion bill defeated on safety grounds

In a Senate Health and Human Services Committee hearing at the Capitol on Feb. 28, a bill was defeated that would have allowed optometrists without the necessary training and education to perform complex laser eye surgeries. The bill was defeated by a one-vote margin.

The South Dakota Academy of Ophthalmology led a mobilized grassroots network of physicians to make sure legislators understood that SB 87 would leave patient safety at risk.

Physician assistant independent practice bill defeated

A proposed bill that aimed to change South Dakota law and remove physician supervision of physician assistants was previously defeated. Through the Coalition and other physician organizations' efforts, legislators understood that this bill would have left patients vulnerable to serious risk.

Thank you!

The defeat of these bills was a result of collaborative, multispecialty efforts, communicating with legislators to express why these bills would have negatively affected patient care.

What's next?

The Coalition is fighting legislation like this that can result in threats to patient safety, and will continue to work to ensure that physicians remain the leaders of health care teams, which is what patients want -- and need.

SDSMA and coalition members will receive updates and alerts from the coalition, including information about scope-related issues.

SOUTH DAKOTA Coalition for Excellence in Patient Care

The South Dakota Coalition for Excellence in Patient Care is made up of the following organizations:

Aberdeen District Medical Society
Black Hills District Medical Society
Huron District Medical Society
Madison-Brookings District Medical Society
Mitchell District Medical Society
Northwest (Mobridge) District Medical Society
Pierre District Medical Society
Sioux Falls District Medical Society
South Dakota Academy of Family Physicians
South Dakota Academy of Ophthalmology
South Dakota Chapter, American Academy of Pediatrics
South Dakota Chapter, American College of Physicians
South Dakota Psychiatric Association
South Dakota State Medical Association
South Dakota Society of Pathologists
South Dakota State Orthopaedic Society
Watertown District Medical Society
Yankton District Medical Society

SDSMA Meets with Congressional Delegation

SDSMA members and staff met with Sen. John Thune, Sen. Mike Rounds, and a staff member from Rep. Dusty Johnson's office on Feb. 14. The meetings took place in conjunction with the American Medical Association's National Advocacy Conference in Washington, D.C.

Meeting with the congressional delegation allows a great opportunity to weigh in on federal issues of importance to South Dakota physicians and patients. Topics of discussion included Medicare physician payment reform and its impact on patient access, scope of practice, and graduate medical education funding.

Attending the meetings were Lucio N. Margallo II, MD — SDSMA President; Mary S. Carpenter, MD — Delegate to the AMA; Robert J. Summerer, DO — Alternate Delegate to the AMA; and Barb Smith — CEO.

Drs. Lucio N. Margallo II, Mary S. Carpenter, Robert J. Summerer, and SDSMA CEO Barb Smith met with Sen. John Thune.

Drs. Lucio N. Margallo, Mary S. Carpenter, and Robert J. Summerer met with Sen. Mike Rounds.

Drs. Robert J. Summerer, Mary S. Carpenter, and Lucio N. Margallo II at the AMA National Advocacy Conference in Washington, D.C.

SDSMA Signs on in Support of Prior Authorization Reforms

South Dakota State Medical Association, American Medical Association and 118 medical societies united in strong support of the meaningful prior authorization reforms proposed for Medicare Advantage and the Medicare prescription drug benefit.

The physician organizations sent a letter to Administrator Chiquita Brooks-LaSure thanking her and urging the Centers for Medicare & Medicaid Services (CMS) to finalize proposed prior authorization reforms that target the inappropriate use of authorization requirements by Medicare Advantage plans to delay, deny and disrupt the provision of medically necessary care to patients.

A recent AMA survey found more than 9 in 10 physicians (93%) reported care delays while waiting for health insurers to authorize necessary care. More than 4 in 5 physicians (82%) said patients abandon treatment due to authorization struggles with health insurers, and more than one-third (34%) of physicians reported that prior authorization led to a serious adverse event, such as hospitalization, disability, or even death, for a patient in their care.

PATIENT EDUCATION:

Extending the Golden Hour

Debra Johnston, MD

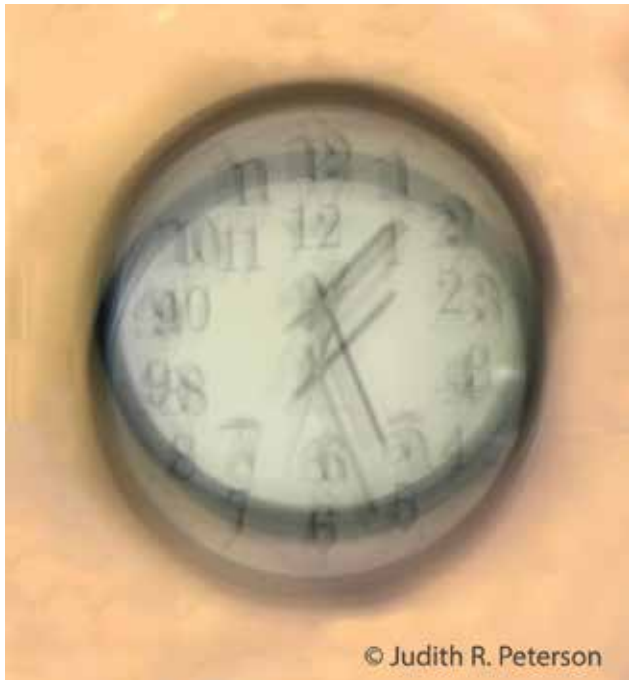
When I was a young physician, we talked with almost religious zeal about the "Golden Hour." Early on, this principally focused on the idea that within the first hour after an injury, a patient needed to receive definitive treatment in order to maximize the chances of survival, and recovery. We usually interpreted this to mean that the patient needed to be in the hands of the trauma surgeon before this hour was up. We took ATLS classes so we could make sure that the patient in our emergency room got the best treatment we non-surgeons could provide, until the surgeon could take over.

Of course, in the rural upper midwest, the nearest surgeon, and even the nearest emergency room, might be more than an hour away.

Fortunately for those of us living in more sparsely populated areas, time to the surgeon isn't the only factor that impacts our chances in an emergency. The care we receive before we get to the hospital matters. In fact, it matters a lot.

Gone are the days of "scoop and run" when the only goal of the first responders was to get the patient to the hospital as fast as possible. As with so many roles in modern society, a first responder today has a more complicated job. They need the training and flexibility to address what they see when they meet their patient. A person who has overdosed on fentanyl needs naltrexone, to reverse the opioid and get them breathing. A person in cardiac arrest needs a shock delivered, to restart their heart. A person who has lost a limb in a car accident needs the bleeding stopped. These things need to be done well before the patient could arrive in an emergency room, even if they were delivered there by helicopter.

Certainly some emergencies require care that is still well beyond what could be provided outside of a hospital. If they can receive it in time, approximately 25% of stroke victims could benefit from clot busting medications. Another 10-15% have strokes that are actually caused by bleeding. It's



a distinction that can't be made in an ambulance, and the wrong call could be catastrophic.

We all know that the pandemic has radically changed the workforce. Employers around the country are facing a shortage of workers, from fast food to finance. Health care is no different. This includes ambulance services, where the situation is further complicated by the reality that many rural EMS providers rely on volunteer labor. Those volunteers need to know more than just how to drive the ambulance. They need to know how to provide effective interventions, to extend that "Golden Hour." This particular labor shortage has grave consequences. It is quite literally a matter of life and death.

Debra Johnston, M.D. is part of The Prairie Doc® team of physicians and currently practices family medicine in Brookings, South Dakota. Follow The Prairie Doc® based on science, built on trust, at www.prairiedoc.org and on Facebook featuring On Call with the Prairie Doc® a medical Q&A show, broadcast on SDPB and streaming live on Facebook most Thursdays at 7 p.m. central.

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We can help anyone 13+ quit vaping too. To find out more, visit **sdquitline.com/providers**

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*Truth Initiative Survey, January 2021

A PUBLIC HEALTH MESSAGE FROM THE SOUTH DAKOTA DEPARTMENT OF HEALTH

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