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Number 3

South Dakota medicine

THE JOURNAL OF THE SOUTH DAKOTA STATE MEDICAL ASSOCIATION

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WHY SHOULD YOU HAVE A BUDGET?

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KADIN WHITE, CFP®, CHFC®, Lead Advisor

The word, budget, can induce fear and anxiety for some people. It could be the notion that budgets are meant to restrict spending. To others, it might feel like a tedious, rigid, time-consuming process. It could be a fear of losing flexibility in their spending patterns. Maybe they'll have to put off purchasing that new car or the summer vacation. If all those things were true, it would be easy to see why so many people might avoid starting the process altogether. But I would argue that creating a budget and being disciplined in the process creates more freedom and flexibility than the alternative. It can be a tremendous vehicle to accomplish long term financial goals. Creating a budget can offer so many benefits. I have outlined a few below.

Financial Control

If you have a good understanding of where you spend your money, you can set yourself up to make informed decisions. It's not about spending restrictions but about empowering you to spend money on the things that matter to you.

Stress Reduction

According to the American Psychological Association Survey, 72% of American report feeling stressed about money.[1] The process of creating and maintaining a budget could lead to lower stress levels. Once you have a firm understanding of your income and expenses, you'll likely find room in your budget to increase savings, pay off debt, or get that emergency fund finally set up.

Improved Communication

In families and partnerships, effective communication should be a high priority. According to the National Library of Medicine, 38% of divorces are due to financial problems.[2] Setting aside time to talk through the family finances could improve transparency and build trust.

Increased Savings and reduction in debt

The typical downstream effect of a budget is increased savings, debt reduction, and progress toward financial goals. By having a firm grasp on your finances, you'll likely find ways to reduce frivolous spending and put those dollars to better use.

Where to Start?

It could be as simple as taking time to write down your income and fixed expenses. I'm a big fan of leveraging technology when it comes to creating and managing a budget. There are some wonderful tools on the market that can help you through the process and save you valuable time. Another method that certainly helps is to seek professional help through a financial advisor. If you need help thinking through a budget, or getting a better handle on your finances, reach out to our team. We would love to help!

[1]https://www.apa.org/news/press/releases/stress/2014/financial-stress

[2]https://www.forbes.com/advisor/legal/divorce/divorce-statistics/

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Pillar 2: A Steep Hike With a Worthy Payoff

Alan Sazama, MD

There is a great hike in the Grand Tetons in Wyoming to a beautiful mountain lake known as Delta Lake. As my friend and I set off, we knew several miles and hours awaited what undoubtedly would be a beautiful payoff. Several miles of steep back and forth uphill hiking left us exhausted as we came to a field of boulders which required careful navigation. When we got done with that, now several hours in and exhausted, an incredibly steep and slippery final mile awaited us. As Pillar 2 Director for the Sanford School of Medicine, I see our students go through a similar trajectory in their medical school journey. Pillar 1 is rigorous and challenging, pushing students to a capstone that requires careful navigation, USMLE step 1. Before students can really catch their breath, another very steep challenge awaits, Pillar 2. In this article I hope to give you some semblance of what Pillar 2 looks like for the typical medical student, what to expect from a student, and what our expectations as a school are for this period of medical training.

Pillar 2 is a 12-month intensive clinical experience consisting of the core clerkships. For many of us who have gone through medical school, this is synonymous with the traditional third year of medical school. What you may find different is that our school utilizes a particular style of curriculum known as LIC (longitudinal integrated curriculum). Rather than traditional clerkship blocks of 4 to 8 weeks, students are immersed in all specialties at once. While foreign to many of us who went through the process, our students have found success in this model, and we continue to graduate high quality physicians who are well respected by their residency program directors.

Students in Pillar 2 have many responsibilities. With the move of USMLE Step 1 to pass/fail, there is growing pressure to boost their application file with research opportunities, case reports, and volunteerism. If there are any sorts of opportunities that you as faculty may have, or could use help with, please let us know at the school – there is likely a student who'd like to be helpful! Students additionally must log procedures and patient encounters in something called SPEL (student patient experience log). You may hear a Pillar 2 student ask to follow you specifically for a day to complete their SPEL log as our clerkship directors have set certain numbers of procedures and patient types to see.

In addition to the clinic time, students also have supplemental parts of the curriculum to work through during Pillar 2, including ethics, palliative care, cultural diversity, radiology, special topics in medicine, and of course exams. Twice a year, our students take a week to take an exam in each of the seven core disciplines of our LIC. They also take OSCE (objective structured clinical examination) four times yearly, two of which are graded encounters and two are provided for formative feedback. They also take an exam known as the CCSE (comprehensive clinical skills exam), a preview of sorts for USMLE Step 2 twice a year. With all these exams we aim to gauge student progress and competence throughout the course of Pillar 2.

As you can likely tell, Pillar 2 is a very busy and demanding period of our medical students' training. Our standard and expectations are high from school administration. We want our students to be exposed to and to experience not only clinical experiences but also the rigor and perseverance required of a career in medicine. Residency awaits so we want our students to be prepared for that experience. Our school has resources for the students to support them through this rigorous training as we know well that burnout has permeated throughout our field. As I am nearing my first cohort being complete as Pillar 2 director, I have observed the payoff at the end of this steep hike is enormous. Our students are excelling and growing as people and future physicians. Seeing this growth truly injects excitement not only in my role at the school but also in my clinical practice in emergency medicine. The education you help provide at Sanford School of Medicine is vital and making a difference in our students' journey and impacting countless lives of their future patients. Oh, and Delta Lake.... also totally worth the hard steep hike. A must see for any outdoor enthusiast!

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Alan Sazama, MD, Pillar 2 Director and Asisstant Dean, Medical Student Education, University of South Dakota Sanford School of Medicine; Avera Medical Group Emergency Medicine, Sioux Falls, South Dakota.

SDSMA Takes to the Hill to Advocate on Medicare Improvements and Other Key Legislation

Denise Hanisch, MD
President, South Dakota State Medical Association

In February, I was privileged to accompany our American Medical Association delegate, Dr. Mary Carpenter, alternate delegates, Dr. Robert Summerer and Dr. Robert Allison, along with SDSMA CEO Barb Smith, to Washington, DC where we attended the AMA National Advocacy Conference. I am thankful for their guidance and mentorship in a world where my experience is limited.

I was reminded several times that advocacy is often a slow and laborious process. It's easy to get frustrated and give up but purposeful consistency is key. Repeated messages to legislators that are concise and relevant are the best way to plant seeds about issues that are important to our patients and our practice of medicine.

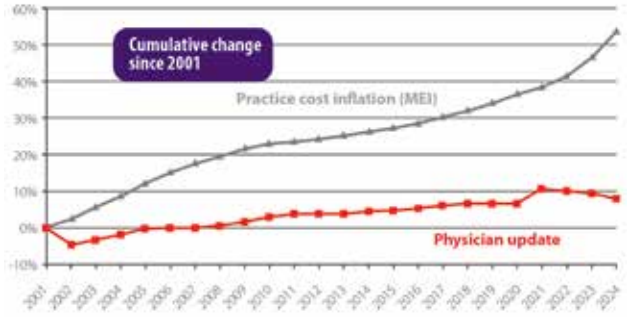
While in DC, we were able to visit with the office staff of our congressional delegation – Sen. Mike Rounds, Sen. John Thune and Rep. Dusty Johnson. Trust that your South Dakota AMA delegation was able to relay concerns regarding several issues including Medicare reform and increasing graduate medical education opportunities.

During the conference, we had the opportunity to hear from several members of Congress and others regarding matters related to physicians, most importantly Medicare reform. There is bipartisan support for changes regarding the way physicians are reimbursed by Medicare. This would potentially improve the way private payers also reimburse physicians as they often follow in the footsteps of Medicare.

Mary Carpenter, MD; Denise Hanisch, MD; Robert Summerer, DO; Robert Allison, MD; and Marty Allison, MD in Washington, DC.

Obviously, we heard from the supporters of reform and their words were promising, but the current stagnation of physician reimbursement will take years to resolve. Currently, the new Medicare adjustments will provide an approximate 3% increase for hospitals, inpatient and outpatient, ancillary services and hospice, while physician pay will decrease by the same 3%. Physicians are the only players in the healthcare market that will see a substantial decline and this is after 20 years without an increase to match inflation (Figure 1).

Figure 1. Medicare updates compared to inflation in practice costs (2001–2024).



Note: Adjusted for inflation in practice costs, Medicare physician payment declined 30% from 2001 to 2024.
American Medical Association

The cost of maintaining a private medical practice has increased 54% between 2001 and 2024, but physician pay has been cut by 30%. Dr. Bruce Scott, president-elect of the AMA, provided an example in his ENT practice. Payment to his practice for a tonsillectomy is approximately $300, which is less than he received 20 years ago, meanwhile, he has had to pay higher costs for staff, rent and other expenses. It would be interesting to hear the opponents point of view regarding sustainability of medical practices with scenarios like Dr. Scott's.

I know the majority of physicians were drawn to medicine because of an unwavering desire to care for people and improve the health of our communities but, we also need to be able to afford to take care of those patients and ourselves. We are more than 20 years behind in making up for what we have lost. This is the time for consistency, perseverance and an unrelenting march forward.

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Auditory and Visual Hallucinations in a Congenitally Deaf Patient with Schizophrenia: A Case Report and Brief Literature Review

Cole Edwards, MS IV; and Jay Weatherill, MD

Abstract

This report discusses the case of a 54-year-old woman with a complex psychiatric history including schizophrenia, tardive dyskinesia, borderline intellectual function, and congenital deafness that reported auditory and visual hallucinations during an acute exacerbation of schizophrenia. After resuming a previous lithium regimen and introducing olanzapine, the patient improved and was discharged without hallucinations. In our report we explore some of the challenges we faced, discuss similar cases, and examine the unresolved debate about whether congenitally deaf patients can experience auditory hallucinations.

Introduction

The hallucinatory experiences of deaf patients with schizophrenia pose a challenge to accurate diagnosis and treatment. Schizophrenia is known to occur in deaf individuals at a rate similar to that of hearing individuals, and several reports published since the mid 20th century suggest that deaf patients endure a similar symptom burden to hearing patients. Debate exists, however, about whether deaf patients experience auditory hallucinations. Here we present a case of a congenitally deaf patient who reported auditory as well as visual hallucinations with the help of a sign language interpreter and her own written responses to written questions. Medical management was relatively straightforward, and the patient improved quickly with the initiation of lithium and olanzapine. However, communication between the patient, providers, and translators was difficult at times and required a tailored approach to treatment. We hope to offer some insights about our experiences to those who might find themselves in a similar situation.

Case Presentation

We report the case of a 54-year-old female patient with a psychiatric history significant for schizophrenia, tardive dyskinesia, borderline intellectual function, and lifelong deafness secondary to congenital rubella infection who presented to our behavioral health urgent care department with an array of symptoms that had escalated over the past week including disorientation, tremor, and lethargy. She had been discharged from the behavioral health hospital just two weeks prior on a new regimen of lithium 300 mg twice daily, brexpiprazole increased from 1 mg to 2 mg daily, and valbenazine 40 mg daily.

The provider team had high suspicion for lithium toxicity and measured a lithium level within the therapeutic range at 0.6 mmol/L (ref. 0.6-1.2 mmol/L). There were no signs of neuroleptic malignant syndrome, though suspicion remained high that symptoms were due to antipsychotic side effect. Medications were held and we transferred the patient to the emergency department (ED) for further workup including CBC and CMP, which were unremarkable. The diagnosis of dystonic reaction secondary to brexpiprazole (recently increased from 1 mg to 2 mg daily) was made and symptoms quickly subsided with a single 50 mg IV dose of diphenhydramine. The patient was then transferred back to the behavioral health hospital and admitted.

Discussions with our patient were aided by a remote ASL interpreter accessed via video and the use of written questions and responses. At admission the patient stated that she was feeling better following stabilization in the ED and having held psychiatric medication. Despite this improvement, though, she reported in writing, "I feel loud," when asked about whether she was experiencing hallucinations. Our efforts to clarify what she had meant by this were met with understandable frustration and we were unable to further characterize the hallucination. Medications continued to be held for another day.

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She would spend the next day sitting alone near a window, displaying repetitive signing patterns in response to internal stimuli which our translator couldn't interpret. She slept very little and stated that the hallucinations were interfering with sleep. We once again asked about the content of these hallucinations, and she stated that she was "hearing voices of angels and demons in my head." Our interpreter verified that she had meant to say "hearing" and the patient confirmed this. She was started on olanzapine 10 mg at bedtime. This was increased to 15 mg qHS the next day due to continued hallucinations and response to internal stimuli.

The patient was no longer responding to internal stimuli by day four of admission but continued to endorse hallucinations. At this point she stated that her hallucinations were more visual in nature, and that she was "seeing" sign language. These statements did stand in sharp contrast to her accounts of having auditory hallucinations less than two days prior. She continued to improve and was restarted on lithium 300 BID on day six of hospitalization, as this had been effective in the past. Olanzapine was finally increased to 20 mg qHS at this time. Symptoms were soon minimal following the re-initiation of lithium and optimized dose of olanzapine, and she was discharged in stable condition with no hallucinations three days later. Her hospitalization lasted nine days in total.

It is worth noting that our attempts at communicating by video or handwriting were sometimes challenging to the patient and led to frustration. Encounters often consisted of a handful of brief, focused questions, and some responses were difficult to interpret.

To the authors' knowledge the patient has remained stable on her discharge regimen of lithium 300 BID, olanzapine 20 mg qHS, and hydroxyzine 25 mg PRN. She has not had symptoms of medication side effect and has not had overt hallucinations. She has been followed closely as an outpatient by providers at home in a neighboring state.

Discussion

Schizophrenia is a complex disorder with a multifaceted etiology, the understanding of which has long challenged psychiatrists, psychologists, and researchers in the field of neuroscience. Evidence suggests that the condition occurs in deaf patients at roughly the same rate as in hearing patients, which raises questions about the essential nature of the condition and the subjective experiences of affected patients.[1] Despite these interesting and unanswered questions, providers must remain comfortable treating deaf patients and work to develop new assessment strategies when verbal communication is not an option.

Contemporary evidence strongly suggests that genetic factors predispose some individuals to developing schizophrenia.[2] These genetic predispositions may be modulated by environmental factors such as cannabis use, developmental abnormalities including *in utero* infection, low socioeconomic status, and past trauma.[3] Deaf patients encounter these stressors at a rate disproportionate to hearing individuals and are also more likely to endure mental health challenges, with some estimates showing that over one-quarter of deaf individuals carry a diagnosis of anxiety or depression.[4-6] It might follow, then, that schizophrenia should occur in deaf patients at higher rate than the general population, but observations since the mid-20th century have consistently estimated that deaf and hearing patients develop schizophrenia at a similar rate.[7,8] If these estimates are to be believed, they suggest that environmental stressors predisposing to schizophrenia then must be *shared* by deaf and hearing patients, and that the unique challenges faced by deaf patients do not actually increase the likelihood that one will develop the condition. Among these indiscriminate environmental stressors are poverty, poor education, inadequate familial support, and abuse, none of which are unique to a particular group.

Diagnosing and treating schizophrenia in deaf patients can be particularly challenging. Sign language interpreters may not always be available, and patients may not communicate well with an interpreter in times of acute agitation. Further, providers and interpreters alike may be unable to distinguish between coherent signing in an agitated patient and disordered signing in a patient experiencing psychosis. Deaf patients understandably experience frustration when providers fail to comprehend their communication, and this frustration often manifests as repeated, pressured signing of the same message several times over. When paired with impassioned facial expressions, habitually decreased eye contact, or social withdrawal misinterpreted as a sort of negative symptom, the misunderstood deaf patient may be incorrectly assessed as acutely psychotic. Situations like these are not uncommon and have led to the placement of legally mandated mental health holds on otherwise healthy individuals.[9] These medicolegal and ethical consequences of mistreating deaf patients, ill or otherwise, deserve providers' consideration.

Careful effort should be made to understand the character of acute psychosis in a deaf patient who does exhibit signs of schizophrenia. Bias may decrease providers' suspicion

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for auditory hallucinations given these patients' inability to hear, but several published case reports suggest that auditory hallucinations have occurred among congenitally deaf patients.[10,11] These accounts also report a common visual type of hallucination in which the patient "sees" or "feels" sign language, and some have speculated that this phenomenon is a consequence of auditory-to-visual conversion of hallucination in patients whose subjective experience contains no concept of hearing. Unfortunately, the authors are not aware of any electrophysiologic or imaging studies that have been performed in deaf patients with schizophrenia, and no such studies were ordered for our patient. These investigations might help characterize the nature of auditory hallucinations in deaf patients by identifying the presence or absence of the auditory brainstem responses that would be expected if the patient were "hearing" in the same way that non-deaf patients hear.

The idea that deaf patients cannot experience auditory hallucinations due to their lack of experience with hearing has led some to argue that the reports of such phenomena are a product of providers' misinterpretations.[12] Those who hold this view further explain that patients universally labeled as "deaf" may experience a wide range of hearing loss and that some patients may be able to hear to a degree. Also, they argue that it is difficult to say for certain that patients described in case reports have been unable to hear since birth, given that definitive testing in past decades was often not performed until the child was many months or years of age. While this intriguing phenomenological debate remains unsettled, it invites further contributions from psychologists, philosophers, and our patients themselves.

Medical treatment of schizophrenia in deaf patients is not necessarily different from treatment of hearing patients. As was true in our case, standard antipsychotic regimens are often effective in managing symptom burden. Importantly, though, providers should be aware that monitoring for improvement may be challenging in cases where a deaf patient is unable to clearly express themselves. Providers must pay close attention to observable symptoms as they can serve as helpful analogue measures of improvement. For example, roughly one day after starting antipsychotic medication, we noticed that our patient was no longer signing to herself and had begun to interact with others during the day. It would not be for another day or two before she was able to express her own improvement to providers. Anyone caring for deaf patients with schizophrenia may consider serial use of tools such as the Psychotic Symptom Rating Scale (PSYRATS),[13] the Positive and Negative Syndrome Scale (PANSS),[14] or the Scale for the Assessment of Positive Symptoms (SAPS) to gather consistent measures of symptomatology.[15] These measurement-based tools may greatly enhance standard verbal interviewing techniques as they provide consistent symptom ratings and can often be completed in a timely manner by the patients themselves.

Conclusion

Our case highlights some of the difficulties providers may face when treating psychiatric disease in a deaf patient. Thoroughness and patience in these cases is especially crucial to understanding symptom burden and formulating tailored treatment plans. Further studies might investigate ways to improve communication between providers and deaf patients and develop effective strategies to monitor for symptomatic improvement.

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Brief Provider Education is Associated with Decreased ED Visits by Super-utilizers

Kjerstin Hensley, MD; and Benjamin Aaker, MD

Background: Millions of adult visits to emergency departments (EDs) each year are opioid-related, and those who visit with chronic pain are more likely to be super-utilizers (SUs) of the ED. Although SUs comprise 5% of the general population, they account for 50% of health care expenditure.

Objective: Determine whether brief provider opioid education results in decreased number of SUs and total ED visits by SUs.

Methods: The American Academy of Emergency Medicine's ED Opioid Prescribing Guidelines were presented to five EDs (estimated total 70,000 ED annual patient volume). ICD-10 codes from visits one year before and after the education were evaluated for painful diagnoses and identified patients who fit the definition of SU. Statistical analysis was performed on the data using McNemar's test and Z-scores.

Results: A statistically significant decrease (p=0.0006) in patients who visited the ED more than once after the education compared to prior to the education (n=304) was found. A statistically significant decrease (p=0.0017) in total number of visits after the education (n=268) by SU patients was found. No statistically significant change in visits made by non-SU patients (p=1.9983), nor average number of visits made by SUs (p=0.2320) was found.

Conclusion: Providing opioid education to ED providers was associated with a significant reduction in number of SUs visiting the ED and number of visits made by SUs. Based on average costs of ED visits by SUs, this decrease in visits can be correlated to an estimated savings of over $1 million across five EDs.

Introduction

Painful diagnoses make up five of the ten most common principal reasons patients visit the emergency department (ED).[1] Additionally, non-traumatic, painful diagnoses make up 21.4% of visits to the EDs in the U.S.[1]

Approximately 234 million adult visits to EDs between 2016-2017 were opioid-related, and those who visit with chronic pain are more likely to be super utilizers (SUs) of the ED.[2] There is no consensus for what constitutes an ED SU. A previous, study defined a SU as any patient who visits the ED more than once a year for the same pain complaint.[3] Although SUs comprise 5% of the general population, they account for 50% of health care expenditure.[4]

Among the 91.8 million adults who took pain relievers in 2015, 1.9 million (2%) qualified for a prescription-opioid-use disorder at some point during the year.[5] Opioid-addicted patients are likely to over-utilize the ED.[6] Each day in the U.S., 130 people die of an opioid-related overdose.[7] Substance abuse places an economic burden on the health care system. Increased healthcare needs, lost productivity, costly addiction treatment, and criminal justice involvement are estimated to cost the health care system $78.5 billion annually.[8]

Painful diagnoses are the most common principal diagnoses for SUs.[9] Treatment for one patient's condition might vary widely depending on the diagnosis and provider training. As of 2019, pain management training and continuing medical education (CME) vary by state, with some requiring as much as 100 hours every two years (such as California, Maine, New Hampshire, etc.) to as little as no required opioid-related CME (South Dakota and Montana).[10]

One suspected reason for variability in treatments for pain is a limited knowledge of guidelines regarding prescribing opioids among ED providers. A study at a rural ED in South Dakota found that educating ED providers with the American Academy of Emergency Medicine (AAEM) opioid-prescribing guidelines was associated with a decrease in total

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visits by SUs and the total number of SU patients.[3,11] Our study hypothesized that by providing clear opioid prescribing guidelines to ED providers, a decrease in SUs and visits made by SUs would be observed.

Materials and Methods

This project investigated SUs from the EDs of five hospitals which are part of the Avera Health system in the Midwest U.S. The hospitals have been de-identified (hospitals A-E), and the range in patient volume in the ED per year is 7,000 – 37,000. The institutional review boards (IRB) of the University of South Dakota and the Avera Health system approved this project. Informed consent was not required for this study.

Study Design

This study was divided into three phases. In Phase I, education was presented to emergency providers (EPs) at the five hospitals included in this study. In Phase II, data were gathered one year prior and one year post Phase I. In phase III, data were analyzed by the investigators.

Phase I

The educational intervention consisted of a review of 2013's (AAEM's) Model ED Pain Treatment Guidelines.[11] Between August 2020 and October 2020, the investigator used PowerPoint (Microsoft) slides to discuss the guidelines. Staff not in attendance received the PowerPoint slides of the education via email. No follow up education was provided. Due to constraints of the COVID-19 pandemic, the presentation venue was selected by each ED's administrator.

Table 1 shows selected guidelines. The educational intervention presented the complete guidelines, and the attendees could ask questions and offer comments. The guidelines were presented as informational, and the attendees were informed that utilization of the guidelines was not mandatory. No attempt was made to assess for comprehension or intention to use the guidelines.

Phase II

The Avera Medical Records Department provided the investigators de-identified Excel spreadsheets (Microsoft) of every patient who visited each of the five EDs one year prior to and one year post the education at each department. Also included in the spreadsheets were the patients' final diagnoses as ICD-10 codes.

A SU was defined to be any patient who visited the ED and received a final diagnosis of a painful condition in the same body area more than once in a year. To determine if the final diagnosis of a patient for their visit was considered a painful diagnosis, the principal investigator selected painful diagnoses limited to specific body areas. Only patients who visited the ED multiple times for a diagnosis in the same body area were included. Patients who visited the ED multiple times, but for different body areas, were removed.

Table 2 shows the list of body areas and problem types. The 'Other' category includes generalized painful diagnoses.

Table 2. Body areas/problem types.

Abdomen	Dental	Head	Other
Acute pain	Ear	Headache	Post-op
Anus/rectum	Eye	Joint	Psych
Arthritis	Face	Limb	Spine
Bone	Female	Male	Substances
Chest	Gout	Neuro	Throat
Chronic pain	GU	OBGYN	

Phase III

Data were analyzed in Phase III. SU use of the ED was assessed by total number of patients and by total number of patient visits. For instance, one patient might have visited twice, while another might have visited 20 times, but both would be considered a SU if each of their visits were for the same painful complaint. To assess the number of patients, McNemar's test was run for each hospital and all hospitals combined to compare the data before and after the intervention. Probability values equal to or lower than 0.05 were considered statistically significant. The change in number of visits by SUs and visits by non-SUs before and after were evaluated by finding a Z-score. This assessed if

Table 1. AAEM: ED Opioid Prescribing Guidelines for the Treatment of Non-Cancer Related Pain[11] (key points).

Prescribe a short course (up to three days) of opioid medication for most acute pain conditions.
Consider accessing a centralized prescription network or state-based prescription drug monitoring program, when available, for patient information on recent controlled substance prescriptions.
Refrain from replacing prescriptions for lost, stolen, or destroyed opioid prescriptions.
Refrain from refilling chronic opioid prescriptions. Refer the patient to the treating clinician who provided the original prescription.

For a complete list of the guidelines, see references.

there was a change in visits by our target population, SUs, and non-SUs.

Results

Data were categorized by each hospital and by all the hospitals combined. The change in number of SU patients one year after the intervention compared to one year prior to the intervention is reported in Table 3. The change in number of visits by SUs one year after the intervention is reported in Table 4.The change in number of visits by non-SUs is reported in Table 5. A Z-score and p-value were calculated to assess change from prior to the invention to after the intervention.

Table 3. Increase/decrease in SU patients who visited more than once at each hospital and in total for the same painful diagnosis (a negative value denotes a decrease).

Change in SU patients		
Hospital	Change in patients	p-value
A	48*	0.0474
B	-54	0.1618
C	-70*	0.0086
D	-210*	0.0011
E	-18	0.5665
Combined	-304*	0.0006

Table 4. Increase/decrease in visits made by SU patients at each hospital and total (a negative value denotes a decrease).

Greater or fewer visits by SUs		
Hospital	Change in visits	p-value
A	141	0.9999
B	13	0.0786
C	-182*	0.0145
D	-449*	0.0001
E	209	0.9899
Combined	-268*	0.0008

Table 5. Increase/decrease in visits made by non-SU patients at each hospital and total (a negative value denotes a decrease).

Greater or fewer visits by non-SUs		
Hospital	Change in visits	p-value
A	-898*	0.0001
B	183	0.9210
C	-117	0.9855
D	443	0.9999
E	97*	0.0101
Combined	-292	0.9992

Discussion

There was a statistically significant decrease in the number of SU patients from all the hospitals combined who visited the ED more than one time for the same painful diagnosis. This may show that certain SUs found improvement in their pain after their visit to the ED or found other avenues for treatment.

Data were stratified further into those who visited greater than 2 times (p-value = 0.5412 and greater than 3 times (p-value = 0.8898). There was no significant difference in the total SU patients in either group. This is perhaps because those patients with many more visits per year were unaffected by the intervention and skewed the results.

Our study has some limitations. There was variability between hospitals. This may have been due to hospitals being located in different states (Minnesota and South Dakota) and having different requirements during the COVID-19 pandemic.[12] Also, the format of the education varied among hospitals (in-person or virtual). We did not confirm receipt of the educational materials for those who received education by email.

The statistically significant decrease in visits by SUs likely led to a decrease in cost to the hospitals. The cost of an ED visit by a SU has been estimated to be $2,700-$5,000.[9] If the average $3,850 is used when looking at the total decrease in number of visits by SUs, 268 visits, that is an estimated savings of $1,031,800 to the hospital system.

Educating EPs on AAEM's ED Opioid Prescribing Guidelines was associated with a significant reduction in number of SU patients visiting five Midwestern EDs. Further, the statistically significant decrease in total visits by SUs can be correlated to monetary savings by the hospital system, insurance providers, and patients.

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South Dakota Dermatology: Urban vs Rural Wait Times and Dermatologist Density

Colby Felts, MD; Lauren Ochoa, MS IV; and Marcus Frohm, MD

Abstract

Background: As of 2019, South Dakota had only 32 registered dermatologists, one per 27,569 people. Wait times for dermatologic care are affected by factors such as socioeconomic status, provider distribution, and patient to provider ratios. This inaccessibility to care or prolonged wait times may lead to diagnosis and treatment delays as well as disease progression. We hypothesized wait times to see a dermatologist would be longer in rural areas than urban areas in South Dakota.

Methods: Dermatology clinics throughout South Dakota were contacted to obtain wait times. An internet search was conducted to develop a list of dermatology providers. A population of 50,000 or greater defined an urban area and a ratio of four dermatologists per 100,000 people was used as an ideal patient to provider ratio.

Results: Overall, 75% of South Dakota's dermatology clinics participated with an equal rural to urban distribution. There was no difference in wait times for new (p=0.787) or established patients (p=0.461) comparing rural and urban clinics. All South Dakota cities with clinics met the goal patient to dermatologist ratio except for Dakota Dunes (included as part of the Sioux City, Iowa, metro population).

Conclusions: The data does not support the hypothesis that wait times for dermatologists would be longer in rural locations than urban locations. Despite adequate dermatologist to patient ratios throughout most of South Dakota, wait times of over six weeks were found at both urban and rural locations, indicating the need for future studies to assess potential solutions for improving timely access to dermatologic care.

Introduction

As of 2019, South Dakota had 32 registered dermatologists, one per 27,569 people. At that time, the state population was 882,235 and continues to rise.[1-3] The state's dermatologic disease burden is shared by dermatologists with primary care providers (PCPs), a ratio of one primary care physician (819 total) per 1,077 people.[1] For this paper, we included dermatologic advanced practice providers (APPs) (physician assistants and nurse practitioners) in the definition of dermatology providers along with dermatologists.

The dermatologist to patient population ratio varies throughout the U.S. According to the American Academy of Dermatology (AAD), 38.6% of dermatologists practice in the 100 most population dense zip codes, compared to only 1.8% practicing in the 100 least dense zip codes. Although dermatologist numbers have steadily increased, 70% of zip codes in the U.S. with at least one dermatologist still have a ratio of less than 4 dermatologists to 100,000 patients (one per 25,000 people), the ideal minimum ratio for adequate care.[4] The mean U.S. dermatologist to population ratio is 1.1 per 100,000 people with only 12% of the U.S. population having a dermatologist to population ratio of ≥ 3.5 per 100,000 people.[5]

For this paper, any city with a population of 50,000 or more was considered urban and a population of less than 50,000 was considered rural.[6] Of counties designated as "rural" by the U.S. Census Bureau, 88% have zero dermatologists.[5] An alternative definition of rural categorizes counties on both population and population density. Of South Dakota's 66 counties, 30 are rural (less than 65,000 people) and 34 counties are even less populated being labeled frontier (less than six people per sq. mile).[6,7] Only Pennington and Minnehaha county are urban with each containing cities with populations greater than 50,000 (Lincoln County continues to grow in size as the Sioux Falls metro area expands and approaches urban status).[8] This data provides important context when assessing South Dakotan's rural population

and access to dermatologists.

Wait times to be seen for dermatologic care are affected by factors such as socioeconomic status, provider distribution, and patient to provider ratios. Prolonged wait times can be associated with delayed diagnosis, disease progression, and increased rates of mortality, particularly in aggressive neoplasms like melanoma.[9] Further distance to the biopsy provider has even been associated with increased Breslow depths of melanomas.[10] Data has also shown increased odds of more advanced lesions and poorer accuracy in identifying malignant lesions in rural areas where dermatologic care is frequently provided by PCPs instead of a specialist.[11]

Rural patients may drive significant distances to be seen by providers in urban locations. In one study, patients identified two of the biggest barriers to dermatologic care were geographical distribution and long care delays.[11] A recent study in South Dakota showed 29% of patients at a rural dermatology clinic would be unlikely to travel further for dermatology care.[12] Importantly, the availability of a physician appointment has been found to be a significant predictor of malignant melanoma's stage at the time of diagnosis.[13]

No one has studied the differences in wait times to access dermatologic care between rural and urban areas in South Dakota. The purpose of this project was to identify if there is a difference in wait times to be seen by a dermatologist in rural versus urban areas in South Dakota as well as analyze dermatologist density in the state. Our hypothesis was wait times to see a dermatologist would be longer in rural areas than in urban areas, which would have increased provider to patient ratios.

Methods

The overall goal was to analyze dermatology care in South Dakota utilizing wait times and dermatologist density. To conduct this analysis, dermatology clinics throughout South Dakota were contacted via phone to obtain wait times to see a dermatologist in weeks for new and established patients. Author 2 conducted an internet search of the AAD "Find A Dermatologist" webpage with the search term "South Dakota" to identify dermatology providers. All dermatology clinics and providers listed were verified via Google search. Individual clinic websites were cross-checked to identify other potential providers, including APPs, who were not members of the AAD to confirm all providers were accounted for.

U.S. census data was used for population statistics. Metro populations of 50,000 or greater defined an urban area with Dakota Dunes as part of the Sioux City, Iowa metro area. A ratio of four dermatologists per 100,00 people was used as an ideal patient to provider ratio.[4] The study demonstrated strong validity with comparable results to a previously conducted similar study in Ohio.[16] Nevertheless, the exact validity is unable to be measured given the lack of direct comparison between study designs on the same population in addition to variability with estimated wait times and not having full participation with all clinics in the state. Regarding dermatologist density, there is decreased validity because the analysis assumes all dermatologists are full time employees working five days per week. The reliability of the study is variable given the constantly changing wait times depending on the season, job changes, estimated times, and random variations in patient volume. While multiple samples of wait times throughout the year would provide a more reliable analysis, this was not conducted due to suspected lack of participation.

The target population were dermatology clinics within South Dakota. University of South Dakota Institutional Review Board (IRB) approval was granted with protocol IRB 21-48. Author 2 initially contacted clinics with author 1 following up if a wait time was not obtained for a maximum of two attempts (see Figure 1 for script). The staff individual who answered the phone was provided the script. Dermatology clinics were informed they would only be labeled as rural/urban and no other identifying information was needed. Data was entered into a password protected Microsoft Excel spreadsheet by one investigator which was independently

Figure 1. Phone call script when contacting South Dakota dermatology clinics.

Hello. I am (author states name) and I am a (author states their year of training as a medical student/resident) at the Sanford School of Medicine at the University of South Dakota. I am conducting a completely voluntary research study titled South Dakota Dermatology: Urban vs Rural Wait Times and Dermatologist Density. The purpose of the study is to analyze barriers to Dermatologic care in rural areas.

You have been invited to participate by being a Dermatology Clinic within South Dakota. If you agree to participate, you will be asked for your current wait times for new and established patients to be seen. Your participation in the study is strictly voluntary. You may withdraw from the study at any time for any reason. Your responses will only be correlated to the population your clinic is located in as either rural (<50,000), urban (>50,000), or outreach clinic. You will not be compensated for participating and there are no costs to you. Once again, your participation in this study is completely voluntary and you may withdraw from the study at any time for any reason.

analyzed by the other investigator to ensure accuracy and consistency. Data from non-participating clinics was excluded. For density analysis, Dakota Dunes was the only South Dakota city where the population from a bordering state was included. Density ratios were calculated from only dermatologists and not APPs. The data was analyzed with two tailed, two sample unequal variance t-tests. P values were generated in Microsoft Excel for statistically significant change with $\alpha = 0.05$. Primary outcomes included wait times and dermatologist density.

Results

All dermatology clinics in South Dakota were contacted from May 2022 to June 2022. Of the 16 clinics, seven were classified rural and nine urban. Participation rate was 75% (12/16) with an equal distribution between rural (six) and urban (six). For all clinics, wait times to see a dermatologist were slightly longer for new patients (mean 6.75 weeks, median 6 weeks) than established patients (mean 5.75 weeks, median 4 weeks). Comparing rural to urban dermatology clinics, there was no statistically significant difference in wait times for new (p=0.787) or established patients (p=0.461). Voluntarily, seven clinics also provided wait times to see an APP. This wait time was shorter than dermatologist wait times in five clinics and the same in two clinics. See Table 1 for complete analysis.

A list of dermatology providers practicing in South Dakota was gathered in June 2022. A total of 74 providers were identified with 43 dermatologists (58.1%) and 31 APPs (41.9%). Of the dermatologists, seven offered Mohs micrographic surgery (six urban, one rural) and no fellowship-

Table 1. Wait times and analysis.

	New patients			Established patients		
In weeks	Mean	Median	95% CI	Mean	Median	95% CI
Total, n=12	6.75	6.00	[4.85, 8.65]	5.75	4.00	[2.79, 8.71]
Rural, n=6	6.50	6.00	[3.40, 9.60]	4.67	4.00	[3.09, 6.25]
Urban, n=6	7.00	6.00	[3.55, 10.45]	6.83	4.00	[0.00, 13.68]
p-value	0.787			0.461		

Table 2. Dermatologist density analysis

City	Population[8,14]	Ideal number of dermatologists (per 4:100,000 ratio)	Dermatologists	APPs
South Dakota (SD)	896,164	35.9	43	31
SD + Sioux City Metro	1,045,429	41.8	45*	32*
Sioux Falls	281,958	11.3	21	12
Dakota Dunes	149,265	6.0	2 (4*)	5 (6*)
* Including non-South Dakota Sioux City dermatologists and APPs				
Rapid City	141,979	5.7	12	10
Aberdeen	28,324	1.1	2	1
Watertown	22,722	0.9	1	1
Mitchell	15,631	0.6	1	0
Yankton	15,453	0.6	1	0
Pierre	14,000	0.6	2	1
Spearfish	12,358	0.5	1	1

trained pediatric dermatologists were identified. The majority (83.8%) of providers worked in urban areas (62 total, 35 dermatologists, 27 APPs) compared to rural areas (12 total, eight dermatologists, four APPs). Utilizing a goal ratio of four dermatologists per 100,000 people, South Dakota would require approximately 36 dermatologists for an estimated 2021 state population of 896,164.[8] All South Dakota cities with dermatology clinics met the goal ratio except for Dakota Dunes. The Sioux City metro population (including Dakota Dunes) is approximately 149,265 requiring approximately six dermatologists.[14,15] There are two dermatologists in Dakota Dunes and two in the Sioux City metro area not in South Dakota. See Table 2 for complete analysis. See Figure 2 for a distribution map of dermatology providers in South Dakota and Legend 1 for a color key of county populations.

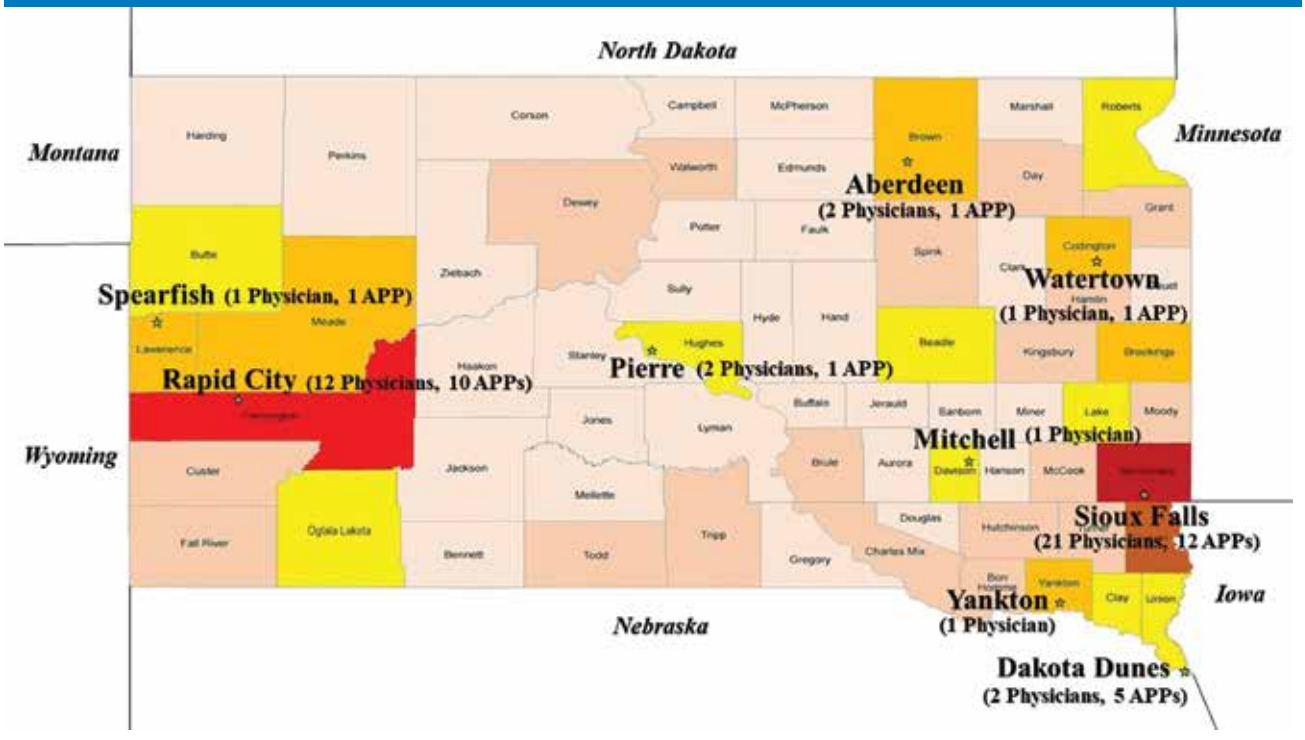
Discussion

This study found no statistically significant difference in rural versus urban wait times to see a dermatologist in South Dakota for both new and established patients. Comparatively, a study examining wait times for dermatology appointments in Ohio found similar results, with no statistically significant difference between rural versus urban settings.[16] Wait times for both new (Ohio 4.5 weeks, South Dakota 6.75 weeks) and established patients (Ohio 3.1 weeks, South Dakota 5.75 weeks) were longer in South Dakota. Contrary to our findings, Suneja's study did find dermatologists in higher population density areas had shorter wait times for new patients.[18]

Although our findings do not support the original hypothesis, the data highlights the critical nationwide problem of prolonged wait times to be seen by a dermatologist. A recent survey of 15 major cities found the average wait time to see a dermatologist was 34.5 days.[19] In another study, 44% of respondents identified long delays for appointments to be their biggest barrier for receiving care.[16] Our data, in combination with these findings, serves to emphasize the need for more dermatologists in South Dakota.

Advanced melanoma (Stage III/IV) carries a devastating prognosis of a 15% five-year survival rate when compared

Figure 2. Distribution map of dermatology providers in South Dakota with county population by color.[17]



Color	Light tan	Tan	Yellow	Orange	Dark orange	Red	Dark red
County population	<5,000	5,000-10,000	10,000-20,000	20,000-40,000	60,000-65,000	100,000-110,000	190,000-200,000

The good news is that patients are more likely to get screened if it is recommended to them by their primary care physician.

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to the 98% five-year survival rate of localized melanoma.[20] Melanomas can quickly progress with studies showing one-third of melanomas growing 0.5 mm in depth or more per month.[21] Given the potential rapid growth, excessive wait times in combination with patient hesitancy to receive care secondary to wait times could be the difference between local and advanced disease.[22]

Recruiting more dermatologists to South Dakota is a complex task influenced by many factors. Further suggestions for improving South Dakota's dermatologic care are additional dermatologic education for PCPs and APPs, improving access at outreach locations, increasing the use of APPs in dermatology clinics, and public education.

The first strength of this study included equal participation from rural and urban clinics with 12 of 16 clinics in South Dakota participating. The second strength was obtaining both new and established patient wait times. The final strength was including the analysis of population density data to providers. This helped determine that even counties with more providers (i.e. Minnehaha and Pennington) still had large patient populations resulting in prolonged wait times.

There were also many limitations. The first is clinics provided an *estimated* wait time which is a subjective measurement with significant variability. These also do not account for triaging patients to be seen sooner with more urgent concerns. The second limitation is not all clinics in South Dakota participated which decreases the power, particularly with the small sample size. This study also cannot assess the volume of dermatologic associated appointments PCPs are managing. Many dermatologists do not work five days per week which skews the dermatologist density data and overestimates the patient to provider ratios. These ratios are also overestimated given patients travel to South Dakota for care given the proximity of clinics to state borders. Lastly, this study does not include the 31 South Dakota dermatology APPs in the analysis.

Future studies are needed to identify barriers to recruiting dermatologists to rural states like South Dakota, estimate the dermatologic disease burden shared with PCPs, and understand the public perception of urgent dermatologic conditions. Given the importance of APPs in areas underserved by physicians, future research could analyze their impacts on overall dermatology care.

Conclusion

The data does not support the initial hypothesis that wait times to see a dermatologist would be longer in rural areas than urban areas. Despite adequate dermatologist to patient ratios throughout most of South Dakota, wait times of over six weeks were found at both urban and rural locations for new patients, indicating the need for future studies to assess potential solutions for improving timely access to dermatologic care. It is necessary for the dermatologic care of South Dakotans that these wait times are decreased, particularly given the risks of delayed care with aggressive skin malignancies.

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MIS-C vs Incomplete Kawasaki's Disease in a 12-year-old Female: A Case Study

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe post-infectious complication of SARS-CoV-2 that seems to occur most frequently two to six weeks after infection. MIS-C can present very similarly to Kawasaki's disease (KD) with symptoms such as a skin rash in addition to a prolonged fever. Here we present a case of a 12-year-old African American/Black female with incomplete KD presenting similarly to MIS-C. The patient presented with prolonged fever, eventually worsening to shock and cardiac dysfunction. We further review the similarities and differences between incomplete KD and MIS-C. Due to their similarities, it is important to keep these diagnoses on the differential when a child presents with a prolonged fever.

Background

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe post-infectious complication of SARS-CoV-2 that seems to occur most frequently 2-6 weeks after infection.[1-7] On May 8, 2020, the CDC issued an alert about the new entity associated with the COVID-19 pandemic.[3] It is characterized by ongoing fever along with vague symptoms including abdominal pain, vomiting, headache, and fatigue.[2,4,5,7] Additional symptoms include conjunctival hyperemia and a skin rash resembling Kawasaki's disease (KD).[1,2,4,5,7]

KD is an acute, systemic vasculitis of unknown etiology that predominantly affects children younger than the age of 5, with a 1.5 times higher risk in boys than girls.[8-10] It is the leading cause of acquired heart disease in children in developed countries.[9] Classically, KD presents as a persistent fever of 5 or more days with at least 4 of the 5 following symptoms: bilateral conjunctival injection, polymorphous exanthema, changes in lips and oral mucosa which is classically known as strawberry tongue, unilateral cervical lymphadenopathy, and hand/foot changes such as erythema, edema, or desquamation.[8] Incomplete KD refers to the presence of persistent fever and abnormal lab values with less than 4 of the above principal symptoms.[11] Another form of KD is known as atypical KD in which patients have unusual manifestations such as renal impairment, pleural effusions, and acute surgical abdomen which are typically not seen in KD.[12] Delay in diagnosis and treatment of KD is associated with significantly higher rates of complications; coronary artery abnormalities may develop on up to 25% of untreated patients.[13]

Case Presentation

A 12-year-old African American/Black female presented to a rural clinic with a 3-day history of fever with a maximum temperature of 40.4° C (104.7° F). She was alert and orientated. She had mild nasal congestion and a cough but denied any other significant symptoms. Vital signs included a plod pressure of 91/43, a heart rate of 128 beats per minute (bpm), and respirations of 16/minute. Physical exam was significant for bilateral lingual tonsil hypertrophy, nasal congestion, and tachycardia.

Lab studies at this time revealed a normal white blood count with a leftward shift (74.1% neutrophils). Molecular assays for influenza A and B, mono-spot test, and COVID-19 PCR were all negative. Initial management with 1L IV normal saline was administered in the clinic. The provider offered cefdinir 250 mg daily as empiric treatment.

After three days of cefdinir, the patient presented to the emergency room with worsening fever and hypotension. She developed fatigue, neck stiffness, worsening tachycardia (141 bpm), increased respiratory rate (24), bilateral conjunctiva injection, and a rash spreading from her extremities towards her chest. Blood cultures were obtained, and the patient was started on norepinephrine and empiric ceftriaxone, and vancomycin. After stabilizing the patient, she was transferred to a larger facility.

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Symptoms progressed to cutaneous peeling around the lips and diffuse swelling in the hands and feet. She did not have cervical lymphadenopathy or swelling of the tongue. Due to suspicion of atypical Kawasaki disease, an echocardiogram was performed and demonstrated mild diffuse ectasia of the left main artery, right coronary artery, and left anterior descending artery with borderline suppression of left ventricular systolic function. There was no aneurysmal dilation. The patient was started on intravenous immunoglobulin (IVIG), aspirin, and methylprednisolone. A second dose of IVIG was administered 36 hours later due to the development of a new fever.

Resolution

Prior to discharge, the patient developed mild congestion and another fever. Blood cultures were negative and she was transferred to a larger regional children's hospital where a repeat echocardiogram was unchanged from prior imaging. The patient continued on ceftriaxone and vancomycin for 48 hours to rule out central line-associated bloodstream infection (CLASBI).

The patient was discharged 12 days after her initial clinic visit with close follow-up with her primary care provider. She was prescribed aspirin 81mg for 90 days. Her most recent echocardiogram was normal. Today she is doing well, with no lasting side effects from her illness.

Methods

The authors performed a literature review on PubMED utilizing keywords such as "Kawasaki," "atypical Kawasaki," "multisystem inflammatory syndrome in children," "MIS-C," "SARS-CoV-2," "typical vs atypical Kawasaki," and "prolonged fever." A systemic Cochrane review was not utilized.

Discussion

Severe COVID-19 infection is much less common in children than in adults. Payne et al. estimated there were approximately 1-10 cases of MIS-C per 1,000,000 SARS-CoV-2 infections.[6] They also identified that MIS-C may disproportionately affect African American and Hispanic or Latino populations in comparison to Caucasian persons.[6] Incidence also varied by age group, being the lowest in those ages 16-20 and highest in those 6-10 years old.[5,6]

The CDC updated the case definition of MIS-C in December 2022.[14] Patients must be aged <21 years old and there is no alternative diagnosis that is more plausible. Patients must have a subjective or documented fever, clinical severity warrants hospitalization or have resulted in death, evidence of inflammation reflected by C-reactive protein (CRP) ≥30 mg/L, new symptoms in >2 of the following: cardiac (elevated troponin, coronary artery dilation or aneurysm, left ventricular ejection fraction <55%), shock, mucocutaneous (rash, conjunctivitis, oral mucosal inflammation, or extremity erythema or edema), gastrointestinal (pain, vomiting, or diarrhea), hematologic (platelets <150K/ µL or absolute lymphocyte count <1000/ µL). Lastly, there must be evidence of SARS-CoV-2 nucleic acid/antigen in the 60 days prior to or during hospitalization or post-mortem sample, OR detection of antibody associated with the current illness, OR close contact with a confirmed or probable COVID-19 case up to 60 days preceding to hospitalization.[14-16] Although the patient in this case did meet most of the criteria for MIS-C, she tested negative for SARS-CoV-2 and an alternative diagnosis was more likely: Incomplete KD.

Patients who meet the CDC criteria for a diagnosis of MIS-C should be observed in the hospital, and depending on severity, may need to be in the PICU.[16] Patients may need supportive care based on their symptoms and clinical status, including but not limited to mechanical ventilation, fluid resuscitation, and vasopressor support. Empiric antibiotics are often given initially, based on patients meeting the criteria for sepsis. These should be discontinued once a bacterial infection has been ruled out.[16] Since MIS-C is still a relatively new entity, it is still being studied to determine the optimal treatment.[1,16,17] It has frequently been treated with IVIG, similarly to KD. Other treatments have included the use of steroids and/or biologics, such as anakinra which is an interleukin-1 receptor antagonist.[16,17] Additionally, all patients without contraindications should be started on thromboprophylaxis with low-dose aspirin. Due to the rapid evolution of treatment recommendations for MIS-C, the American Academy of Pediatrics recommends pediatric subspecialist consultations.[16]

Though the specific etiology of KD is still unclear, an interplay of genetic susceptibility and infectious triggers appears to lead to this abnormal immune response. The highest incidence worldwide is in Japan, occurring in 239/100,000 children under 5 years of age.[8] In the U.S., the incidence of children hospitalized with KD was reported to be 19/100,000 in children younger than 5. The incidence in the U.S. varies greatly with ethnicity. Some reports indicate KD incidence is 2.5-times higher in Asians and Pacific Islanders and 1.5-times higher in Blacks compared to Caucasians.[8,11]

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Although the incidence of incomplete KD is currently unknown, a retrospective report of 242 Japanese children with KD treated at a single center determined that approximately 10 percent qualified for the diagnosis of incomplete KD.[11,13] Incidence of incomplete KD amongst those studied appears to be greater in infants less than six months of age compared to older infants (45% vs 12%, respectively).[18] However, some authors have suggested that the clinical presentations of incomplete KD and complete KD are very similar and may not be 2 different or separate entities, but instead a continuum of disease severity with the current nomenclature being used to describe the severity of the presentation along this continuum.[19] Although not all sequelae for complete KD are met in incomplete KD, children with incomplete KD are still at risk for cardiovascular complications due to coronary artery involvement.[20] During the early stages of KD, neutrophil-mediated necrosis begins to affect the coronary artery walls, known as necrotizing arteritis.[21,22] Neutrophils elastase enzyme that is involved in this process can disrupt the intimal and medial layers of the arteries leading to adventitial damage and eventual aneurysm formation. After the acute phase, a subacute or chronic

Table 1. Comparison of the diagnostic criteria, etiology, ages affected, and treatment of MIS-C and KD.[1,2,4,5,7,8-10,12,15-18]

Diagnostic criteria	**MIS-C** CDC case definition (December 2022) 1. Age <21 years old and absence of more plausible diagnosis 2. Subjective or confirmed fever (T>38°C) 3. CRP ≥30 mg/L 4. Severe illness requiring hospitalization or resulting in death 5. >2 of the following manifestations a. Cardiac (elevated troponin, coronary artery dilation or aneurysm, left ventricular ejection fraction <55%) b. Shock c. Mucocutaneous (rash, conjunctivitis, oral mucosal inflammation, or extremity erythema or edema) d. Gastrointestinal(pain, vomiting, or diarrhea) e. Hematologic platelets <150K/ µL or absolute lymphocyte count <1000/ µL) 6. Evidence of SARS-CoV-2 nucleic acid/antigen in the 60 days prior to or during hospitalization or post-mortem sample, OR detection of antibody associated with the current illness, OR close contact with a confirmed or probable COVID-19 case up to 60 days preceding to hospitalization.	**Kawasaki disease** **Complete KD:** unexplained fever for ≥4 days plus at least 4 of the 5 clinical criteria below **Incomplete KD:** unexplained fever for ≥5 days plus 2-3 of the 5 clinical criteria below 1. Nonexudative bilateral bulbar conjunctival injection. 2. Oral mucous membrane changes, including erythematous and fissured lips, injected pharynx, or strawberry tongue. 3. Peripheral extremity changes including erythema of palms or soles, edema of hands or feet (acute) and membranous desquamation (subacute). 4. Polymorphous exanthema. 5. Cervical lymphadenopathy (at least 1 lymph node >1.5 cm in diameter). **Atypical KD:** reserved for patients with clinical manifestations not in the standard criteria or generally seen with KD such as renal impairment, pleural effusions, and acute surgical abdomen.
Etiology	Preceding COVID-19 infection or exposure	Unknown
Ages	6-10 years	<5 years
Treatment	Supportive measurements, IVIG, steroids, biologics, aspirin	IVIG and aspirin

vasculitis can continue for months to years which involves lymphocytes, plasma cells, and eosinophils and may also lead to aneurysmal formation.[21,22] This process can lead to the activation of muscle cell-derived myofibroblasts, known as luminal myofibroblastic proliferation (LMP). LMP can lead to luminal narrowing with the potential for ischemia or infarction(thang). Slightly dilated arteries may eventually return to their normal size; however, this is less likely with large aneurysms or arteries with intimal thickening.[21]

An echocardiogram is an important diagnostic tool to evaluate for cardiovascular complications. The echocardiogram is considered positive and supports the diagnosis of KD or incomplete KD if any of the following are found: 1) a coronary artery aneurysm, 2) the left anterior descending artery (LAD) or right coronary artery (RCA) is dilated to a Z-score greater than 2.5, or 3) at least three of the following findings are seen: decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z-scores in LAD or RCA of 2-2.5.[15(19)]

Patients meeting the criteria for complete and incomplete KD should be treated as soon as possible. Treatment with IVIG should begin promptly within 10 days of symptom onset.[9] The use of IVIG is critical, studies have shown that in comparison to placebo, there is a significant decrease in coronary artery abnormalities.[9,10] Patients are treated with aspirin along with IVIG.[9,10] The dose of aspirin varies between institutions, but many facilities eventually reduce from high dose to low dose aspirin and continue until there is no evidence of coronary abnormalities 6-8 weeks after illness onset.[9] Up to 10% of patients do not respond to initial therapy and often receive a second infusion of IVIG. Additionally, adjuvant therapies such as corticosteroids, tumor necrosis factor-α, and cyclophosphamide have been used in refractory cases, though their use is not widely accepted or recommended.[9,10] Table 1 compares the diagnostic criteria, etiology, common ages affected, and treatment of MIS-C and KD.

The patient in this case met criteria for incomplete KD as she eventually experienced 3 of the 5 defining symptoms including a polymorphous exanthem (skin rash) on day 3, cutaneous peeling around the lips, swelling of the hands and feet on day 7 plus a fever for 7 days. The echocardiogram findings including mild diffuse ectasia of the left main artery, RCA, and LAD and borderline suppression of left ventricular systolic function also support the diagnosis of incomplete KD. KD is typically noted in children <5 years old which makes this patient's presentation even more unique, thus making a diagnosis on clinical suspicion alone much more difficult. After a review of the literature regarding MIS-C and KD, we believe this is the first case report where incomplete KD initially presented with a prolonged fever with progression to multi-organ involvement similar to MIS-C in a 12-year-old African American/Black female in the U.S.

Conclusion

MIS-C is a rare but severe post-infectious complication of SARS-CoV-2 that resembles KD. MIS-C occurs in patients <21 years old that present with prolonged fever and multi-organ dysfunction approximately 2-6 weeks after SARS-CoV-2 infection. KD on the other hand is typically noted in children <5 years of age with at least 4 of the 5 following symptoms: bilateral conjunctival injection, polymorphous exanthema, strawberry tongue, unilateral cervical lymphadenopathy, and changes of the hands and/or feet. It is important that providers keep KD, MIS-C, or other severe sequelae in mind when evaluating patients with common presentations, such as viral upper respiratory tract infections.

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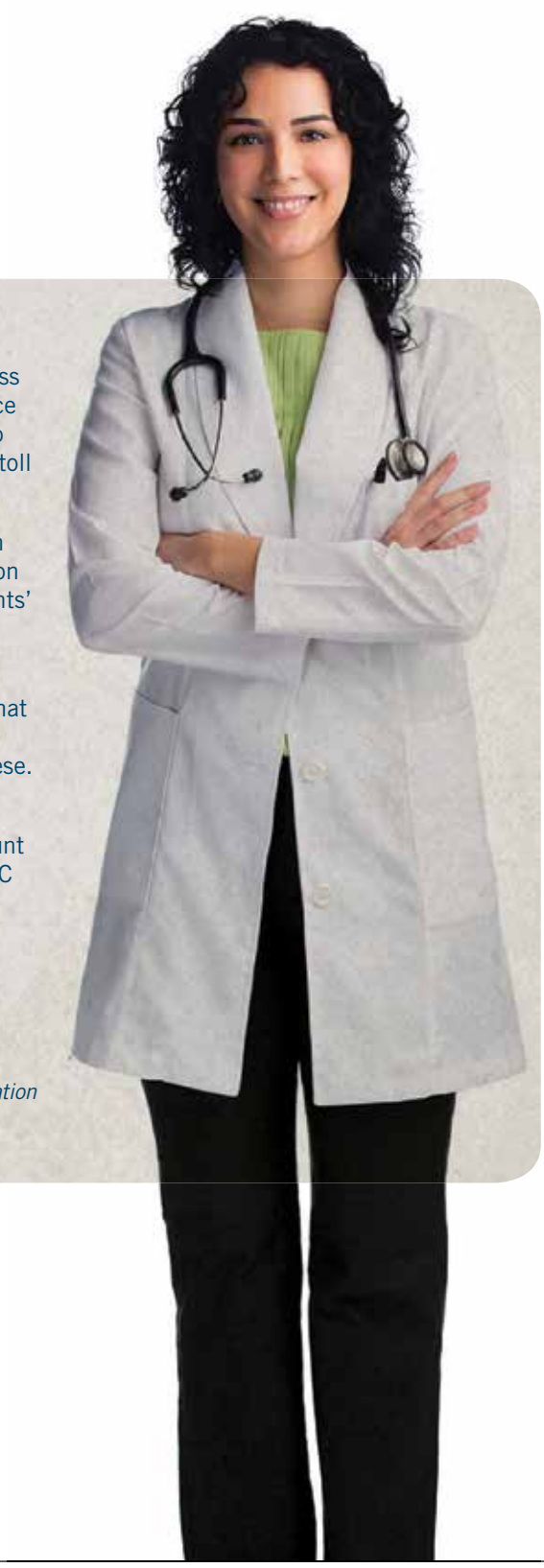

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Overgrowth Disorders: A Case of Sotos Syndrome and Overview of Related Disorders

Joseph Rath, MS IV; Kennedy Forest, MS IV; Allison Hemmer, MS IV; and Matthew Simmons, MD, FAAN

Abstract

Sotos syndrome is an uncommon congenital overgrowth syndrome characterized by excessive growth in childhood, learning disabilities, and distinct facial features. We present the case of a young male who appeared to have the classic presentation of Sotos syndrome despite a normal genetic workup. Additionally, we present a brief review of overgrowth syndromes in order to highlight potential challenges differentiating these syndromes in clinical practice. Many overgrowth disorders often have similar presentation to Sotos syndrome, so it is important to recognize and identify specific clinical features and perform genetic testing to rule out other disorders, confirm a diagnosis, and choose the appropriate management for patients.

Introduction

Sotos syndrome is a congenital overgrowth syndrome with features of excessive childhood growth, learning difficulties, and distinct facial features. The syndrome is associated with haploinsufficiency of the **N**uclear receptor **S**et **D**omain containing protein 1 gene (*NSD1*). Sotos syndrome shares similarities with other overgrowth syndromes, and it can be challenging to establish an accurate diagnosis. Genetic testing and thorough evaluation of clinical features can help diagnose overgrowth disorders like Sotos syndrome.

Case Report

We report the case of a 21-year-old patient clinically diagnosed with Sotos syndrome. His medical history also includes attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), aggressive outbursts, depression, obsessive compulsive disorder, and epilepsy. The history of his diagnosis with Sotos syndrome was a unique journey. His developmental history included a preterm delivery with a one week stay in the neonatal intensive care unit, global developmental delay, and participation in physical, speech, and occupational therapy throughout his childhood. By the age of 5 there was suspicion of Sotos syndrome due to his head circumference (57.2 cm) being greater than the 100th percentile for his age. He also had frontal bossing, a triangular-shaped face, and "lop ears." He had a history of hyperactivity and aggression towards others. He also had a history of petit mal seizures throughout early childhood. Extensive testing for other conditions, including, but not limited to, fragile X, phosphatase and TENsin homolog deleted on chromosome 10 (PTEN) mutations, mitochondrial deoxyribonucleic acid (DNA) mutations, and Beckwith Weidemann syndrome, was negative. Baylor 180K chromosomal microarray, which detects copy number changes with exon-level coverage of 1,700 genes associated with intellectual disability and developmental delay, was also completed with a normal result.[1] Initial *NSD1* sequencing (Sotos syndrome genetic indicator) showed one homozygous polymorphism. The specific polymorphism found indicated to geneticists at that time that there was a potential deletion involving the *NSD1* gene. Follow-up testing with multiplex ligation dependent probe amplification (MLPA) analysis for the *NSD1* gene was normal. This reassured physicians that the *NSD1* gene in this patient was normal. Whole genome and exome testing was considered but has not been completed.

At age 10 a magnetic resonance imaging (MRI) of his brain without contrast was completed which revealed findings consistent with Sotos syndrome including prominent frontal horns of the lateral ventricles, cavum velum interpositum, periventricular white matter changes, and thinning of the posterior body of the corpus callosum. The pituitary gland appeared normal.

Though not all overgrowth syndromes could be ruled out, physicians and geneticists involved in this patient's care performed many tests to rule out other syndromes that are more common and those that present similar to Sotos syndrome. Despite negative testing for genetic markers of Sotos syndrome, at 16 years old he was diagnosed with Sotos syndrome from a clinical standpoint.

Currently the patient is 21-years-old and continues to experience behavioral outbursts and aggression. He also suffers from chronic constipation and megacolon. Additional physical exam findings that align with a Sotos presentation in an adult include acromegalic features and frontotemporal balding. The patient's seizures have been successfully medically managed since early childhood. He is currently following with a variety of healthcare providers to address his diverse set of symptoms.

Discussion

Sotos syndrome is a congenital overgrowth which was identified as a specific syndrome by Sotos et al. in 1964 after observing five patients with similar clinical findings.[2] Until 2002, Sotos syndrome was a clinical diagnosis comprising four major diagnostic criteria: distinct facial features, advanced bone age, macrocephaly, and learning disabilities.[3-5] In 2002, Kurotaki et. al. determined that Sotos syndrome was the result of haploinsufficiency of *NSD1* in more than 90% of cases.[6,7]

The exact birth prevalence of Sotos syndrome is unknown; however, some estimate the incidence to be approximately 1 in 14,000 live births.[4] Due to the relatively low incidence of Sotos syndrome, there is a limited pool of potential subjects for research purposes.[4] Furthermore, this makes it difficult to determine if some clinical features are truly related to Sotos syndrome or mere coincidental findings.[8] More than 95% of individuals with Sotos syndrome are the outcome of *de novo* mutations. Few familial cases with autosomal dominant inheritance patterns have been described.[7,8] Sotos syndrome in patients with a pathogenic *NSD1* variant appears to have complete penetrance, though the expressivity is quite variable, even in those with the same pathogenic variant.[8] Sotos syndrome is not explicitly linked to either X or Y chromosomes, therefore, it equally affects males and females. The *NSD1* gene is located at chromosome 5q35.[4] At this time, it is not entirely clear how *NDS1* haploinsufficiency results in Sotos syndrome.[5,8-10]

Patients with Sotos syndrome tend to have distinct facial characteristics, learning disability, and overgrowth. These three features are known as the cardinal features as they are present in ≥90% of those with Sotos syndrome. Distinct facial features include, but are not limited to, a prominent forehead, dolichocephalic head shape, elongated face, lack of frontotemporal hair, and down slanting palpebral fissures.[4,5,7,8] Learning disabilities vary between affected individuals; it commonly manifests as early developmental delay or mild to severe intellectual impairment. Overgrowth is described as advanced height and/or head circumference, typically greater than two standard deviations above the mean.[4,5,7,8] Characteristic facial features and macrocephaly are most distinctive between one and six years of age.[5,8] Height often normalizes in adulthood, but macrocephaly tends to be present at all ages.[5,8]

Major features which are present in 15-89% of those with Sotos syndrome include behavioral findings (most commonly ASD), genitourinary anomalies, cardiac anomalies, jaundice in the neonatal period, seizures, scoliosis, and advanced bone age.[5,7,8,10] Patients may also suffer from conductive hearing loss secondary to chronic otitis media, gastroesophageal reflux disease, and constipation.[10] There may also be an increased risk of tumors such as sacrococcygeal teratomas and neuroblastomas.[5,10] There is currently no recommendation for tumor screening in patients with Sotos syndrome.[11]

Behavioral concerns tend to be distressing to the individual and the caretakers. Several cognitive and behavioral features have been linked to Sotos syndrome including ASD, ADHD, anxiety, aggression, and emotional outbursts.[4,5,7,8,12] Social inhibition and psychosis have also been observed in some cases.[5] ASD symptomatology tends to be most prevalent in childhood (5-19 years).[12] Behavioral issues may improve with time, but individuals often retain some immaturity into adulthood.[2]

A diagnosis of Sotos syndrome is typically suspected in children less than 6 years of age when excessive height, occipitofrontal circumference (OFC), and/or unique facial features are most prominent.[5] Prior to the identification of *NSD1* in 2002 and its association with Sotos syndrome, the diagnosis was based on clinical features. The four major diagnostic criteria reported by Cole and Hughes in 1994 were overgrowth associated with advanced bone age, macrocephaly, learning difficulties, and distinct facial features.[3] Supporting evidence could be completed with assessment of bone age and/or cranial imaging. Features supporting Sotos syndrome in cranial imaging include abnormalities of the ventricular system and hypoplasia or thinning of corpus callosum. The lateral ventricles are frequently enlarged with prominent trigone and occipital horns.[13]

Today, the diagnosis of Sotos syndrome is established with molecular genetic testing with identification of a heterozygous pathogenic variant or deletion involving *NSD1*.[4,5,6,7,8,9,10] There is no formal clinical diagnostic criteria established for Sotos syndrome, although the cardinal features are often used.[10] One source reports that a patient meeting these criteria but

having negative workup for *NSD1* haploinsufficiency should be given the diagnosis of "Sotos-like syndrome",[4] and others say that a diagnosis of Sotos syndrome can still be given.[8] It is recommended to have the case evaluated by a clinician with adequate experience in overgrowth conditions prior to a clinical diagnosis of Sotos syndrome in an individual with normal *NSD1* evaluation. Patients should also be evaluated to rule out other syndromes and illnesses that may present similarly to Sotos syndrome.[4,8]

A Brief Review of Overgrowth Syndromes

Sotos syndrome is one of many overgrowth disorders that clinicians should consider when patients present with excessive growth and a range of accompanying symptoms.[11] While there are multiple causes of overgrowth including metabolic, constitutional (familial) tall stature, and endocrinopathies, their causes and associated features are not in the same vein as genetic/epigenetic overgrowth syndromes and as such will not be the focus of this review.[11,14] Overgrowth syndromes with a genetic or epigenetic etiology differ due to their range of dysmorphic features often including cognitive impairment and behavioral challenges. Patients with overgrowth syndromes also have an increased risk of tumors, presumably due to the same disrupted molecular factors involved in their abnormal growth.[11,14] These syndromes often have clinical overlap; however, specific features may allow a skilled clinician to distinguish differences between them in order to guide genetic testing and follow syndrome-specific tumor screening programs.[11]

Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is the most common overgrowth disorder (1 in 10,500 births), where 85% of patients have an imprinting disorder in the region of 11p15 controlled by epigenetic mechanisms.[11,14] BWS can be suspected in an infant with the cardinal features of macroglossia, macrosomia, lateralized growth, and abdominal wall deficits, most commonly exomphalos or umbilical hernia.[11,14] These infants typically present with distinct facial features including a prominent mandible, midface hypoplasia, infraorbital creases, and ear pits.[11] The neonatal period can be difficult for those with BWS and the mortality rate is estimated to be as high as 21%, however, those surviving can go on to live healthy lives with normal intelligence. These children also have an increased risk for embryonal tumors, such as Wilms tumor and hepatoblastoma due to deficits in the IGF2 gene found at 11p15.[11] The prevalence of tumors in those with BWS varies, but has been estimated as high as 20%.[11] The risk of developing a tumor is around 7-7.5% higher than the general population.[14] The American Association for Cancer Research (AACR) recommends screening all patients with BWS using abdominal ultrasound to screen for hepatoblastoma and Wilms tumor every three months until the patient is four years old. Ultrasound is then limited to the kidneys to screen for Wilms tumor until age seven. [11,15]

Weaver Syndrome

Weaver syndrome can present similarly to Sotos syndrome with tall stature, large OFC, and advanced bone age. These syndromes have distinct facial features that can help differentiate them.[11,14,16] Distinguishing features of Weaver syndrome are micro-retrognathism with a horizontal chin crease, almond shaped palpebral fissures, ocular hypertelorism, and a broad forehead.[11,14] Additionally, patients with Weaver syndrome may have camptodactyly of fingers or toes. Aside from the clinical features, patients will have a more advanced bone age compared to those with Sotos syndrome[11,14] Patients with Weaver syndrome have mutations in *EZH2*, a gene coding for histone methyltransferase, which is thought to play a role in epigenetically repressing gene expression.[14,17] Mutations in *EZH2* have been identified in tumors and myeloid malignancies, possibly suggesting that *EZH2* may play a role in tumor suppression.[11] However, incidence is less than 5%, and routine screening is not recommended for patients with Weaver syndrome.[11]

Malan Syndrome

The most recently identified overgrowth syndrome, Malan Syndrome, is a Sotos-like syndrome that has mutations or deletions in the *NFIX* gene.[11,18] Clinically these patients will have a slightly increased OFC and a similar facial dysmorphism to Sotos. However, these patients also have traits similar to those of Marfan syndrome including pectus excavatum, ocular abnormalities, and scoliosis.[11,18] Learning disabilities are found in almost all patients with Malan syndrome and can range from moderate to severe.[11] Malan syndrome has yet to be identified as having an increased risk of tumorigenesis and no surveillance is recommended.[11]

Simpson-Golabi-Behmel Syndrome

Simpson-Golabi-Behmel syndrome (SGBS) is an X-linked disorder of the *GPC3* gene located at Xq26.2.[14] The *GPC3* gene product, a heparan sulfate proteoglycan, appears to play a critical role in cell growth and differentiation regulation.[14] A severe form of the syndrome is often lethal in utero, while those with less severe forms are likely to survive into adulthood. Clinically, these patients are over the 97th

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percentile for height and will have features of macrocephaly, macrostomia, macroglossia, ocular hypertelorism, and a broad nasal bridge. Other features of the syndrome may include hand deformities, supernumerary nipples, septal cardiac defects, and cleft lip or palate.[11,14] Intellectual disability is common in SGBS. Embryonal tumor risk is elevated compared to the general population, estimated at 7.5%.[14,19] Current recommendations are to undergo surveillance for neuroblastoma, Wilms tumor, gonadoblastoma, and hepatocellular carcinoma.[11,14] Guidelines recommend urine catecholamines and alpha-fetoprotein every three months until the age of 4, along with abdominal and renal ultrasound every three months until the age of seven.[11,19]

The previously mentioned overgrowth syndromes, along with other syndromes such as Fragile X syndrome, *SUZ12*-related overgrowth, and 22qter deletion syndrome should be considered when diagnosing an overgrowth syndrome. Since these syndromes have varying risk for different malignancies but may appear similar, it is important to correctly diagnose so patients can have proper screening when necessary.

Conclusion

Sotos syndrome is an uncommon overgrowth disorder that presents in childhood with associated learning disabilities and distinct facial features. The patient presented in this case is part of the smaller percentage of individuals who was clinically diagnosed with Sotos syndrome after many years of suspicion and uncertainty due to lack of the *NSD1* genetic anomaly. In cases similar to this, it is important for clinicians to consider all available information and use their clinical and scientific knowledge to establish a diagnosis. The increasing availability of genetic testing has allowed clinicians to more accurately diagnose overgrowth syndromes that are clinically similar, but genetically different. Patients with overgrowth syndromes are at varying risk for development of tumors and malignancy, therefore, it is important for clinicians to establish a diagnosis in order to begin proper screening and surveillance for which they are at most risk.

Literature Search Methods – Information for this review was collected using resources such as PubMed and DynaMed to locate manuscripts from the digital Wegner's Health Science Library. The search was conducted between January and July 2023 and was limited to literature in English. Aside from the publication that initially defined Sotos syndrome in 1964, other articles were limited to a publication date of 1990 or later. Articles were screened by title, then by abstract, and finally, by full text. The literature search for this article was conducted by the authors.

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Congenital CMV in the Neonate: A Primer

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Abstract

Cytomegalovirus, one of the most common congenital viruses in neonates, is represented within the TORCH acronym, which signifies its ability to be transmitted vertically to the fetus during maternal infection. Despite advances in prenatal diagnostics, CMV is still the leading cause of congenital infection in neonates, with a 0.64% prevalence. Additionally, the virus causes the majority of non-genetic hearing deficits, abnormal neurologic development, and other permanent disabilities seen in neonates. This primer describes the presentation, diagnosis, and treatment of congenital infection to benefit providers who work with women during the perinatal period as well as neonates and pediatric patients.

Introduction

Cytomegalovirus (CMV), a double-stranded DNA herpesvirus, is one of the most common congenital viruses among the neonatal population.[1] For this reason, it is represented within the TORCH acronym, signifying its vertical transmission to the fetus in utero during maternal infection. The virus is present in all body fluids, including urine, blood, and cervical secretions, and is transmitted via person-to-person contact.[1] Women of reproductive age often are exposed to and contract CMV from interaction with young children.[2]

The variability and insidious nature of the virus cloud the ability of prevention, detection, and prognosis. While most infants with congenital infections of CMV are asymptomatic, the neurologic deficits and long-term sequelae of severe cases can have devastating and permanent effects on the neonate.[3] Early diagnosis of congenital CMV (cCMV) can expedite treatment and improve outcomes. Thus, it is imperative that clinicians recognize the clinical manifestations early in utero. This article intends to serve as a brief primer on cCMV, highlighting the epidemiology, pathophysiology, clinical manifestations, diagnosis, prognosis, prevention, and treatment.

Epidemiology

CMV infection among women of reproductive age is common, with seroprevalence ranging from 45 to 100%. If primary infection, reactivation, or reinfection occurs during pregnancy, there is potential for transmission to the developing fetus in utero.[4] According to a 2021 meta-analysis of 77 countries that screen infants before three weeks of age, the prevalence of congenital cytomegalovirus was 0.67%. Given this low prevalence, routine screening of asymptomatic pregnant women is not recommended. Additionally, the authors found the infection burden was 3-fold greater in low- and middle-income countries compared to high-income countries. cCMV infection can lead to permanent sequelae in 15% to 18% of births, including death in 1% of cases, neurocognitive sequelae in 5% to 15%, and hearing loss in 12%.[5] It is estimated that of the approximately 40,000 infants diagnosed with cCMV in the U.S. every year, 4,000-6,000 present as symptomatic.[6]

Transmission risk varies during stages of gestation. The risk of transmission during primary infection occurring in the first and second trimesters is 30-40% and increases to upwards of 70% in the third trimester. However, the risk of transmission is much lower (3%) for non-primary infections. If a primary infection occurs during the first trimester, there is a greater risk of complications for the fetus[7]. CMV infection can be transmitted in a variety of ways including breastfeeding, viral shedding in close-contact settings, blood products, and sexual contact. CMV infects between 60% to 70% of adults in industrialized countries and close to 100% in emerging countries.[8]

Prevention of CMV infection primarily relies on decreasing exposure to potential infectious sources, although this is not always possible. A common source of CMV is young children, who are typically asymptomatic. CMV viral particles can be present in a child's body fluids for months after infection. Expecting mothers and people planning to become pregnant can decrease their risk of CMV exposure

by practicing diligent hand hygiene after changing diapers or helping a child use the toilet. Additionally, avoiding sharing food, utensils, or cups with young children can reduce the risk of CMV exposure.[7]

Pathophysiology

During pregnancy, the maternal immune system must adopt a fine balance in order to protect the mother from pathogens in everyday life while also sustaining the pregnancy via fetal tolerance. Decidual natural killer cells activated by cytokines are one of the primary components of the innate immune system that facilitate interactions with trophoblasts via human leukocyte antigens.[1] The other component of the immune system, the adaptive element, weakens the immune system to aid in fetal tolerance through CD4+ regulatory T cells. This mechanism of immune suppression required to maintain a pregnancy, also makes pregnant individuals more susceptible to pathogens during gestation[1].

There are two mechanisms of fetal infection during pregnancy: primary and reactivated maternal infection, the latter being less common and often subclinical. Women with reactivated infections secrete viral particles from the cervix, which inoculate the neonate during delivery. If the infant lacks sufficient maternally acquired antibodies, the infant may become infected.[9] Although most maternal CMV infections in pregnancy are asymptomatic, 10-15% may present with flu-like symptoms, such as fever and lymphadenopathy. In both mechanisms, women will have elevated immunoglobulin G (IgG)1 levels[1]. Although transplacental CMV transmission is possible through viremia in about 1% of seropositive pregnancies, the majority of neonates are infected during delivery via contact with maternal blood, cervical, and vaginal secretions.[1,9]

Development of the fetal immune system begins during the 9th to 15th week of gestation. During the 16th week, the transfer of maternal IgG antibodies drastically increases to reach adult equivalent levels in the fetus by 26 weeks. Maternal IgG antibodies confer passive immunity to the developing fetus[1]. The rate of antibody transmission increases with gestational age. Studies have shown that fetuses in their third trimester have fewer complications than infants infected in their first and second trimesters. For this reason, maternal CMV infection is not an indication for cesarean section.[2]

Clinical Manifestations

While most newborns infected with CMV are asymptomatic, there is a possibility of late-onset sequelae. Those who are symptomatic often present with multiple, severe symptoms identifiable as a syndrome. Presentation of the clinical manifestations of CMV varies greatly, ranging from transient or mild illness to fulminant dissemination with the possibility of neonatal demise.[6] Various studies suggest there may be certain strains of CMV or viral markers that may be predictive of severity, however, more research is needed before this can be used clinically with reasonable reliability.[10] Symptomatic infants infected via vertical transmission often present with a syndrome-like pattern of processes that affect multiple organ systems. The most notable manifestations affect the nervous system, hematopoietic system, liver, spleen, eyes, and overall growth.

Many of the hallmark symptoms of cCMV affect the nervous system and have both early and late-onset sequelae. At birth, microcephaly, intracranial calcifications, germinal matrix cysts, ventriculomegaly, and numerous sensorineural deficits are commonly seen.[1,6] In infants or children who present with late-onset sequelae or who have inconclusive serology with unexplained deficits, neuroimaging is useful in diagnosing cCMV. MRI is the preferred imaging modality given the lack of radiation, although CT imaging may be used if MRI results are inconclusive. The most common clinical manifestations of cCMV on neuroimaging are periventricular calcifications, atrophy of the cerebrum, dilation of the ventricles (Figure 1), and lissencephaly.[11]

Sensorineural deficits are characterized by ocular manifestations and sensorineural hearing loss. Ocular involvement may present as chorioretinitis, cataracts, or optic atrophy. CMV chorioretinitis has been described as having a "pizza-pie" appearance on fundoscopic exam due to retinal hemorrhages (Figure 2).[12] Hearing loss is the most common sequela of cCMV and is seen in both symptomatic and asymptomatic neonates. Sensorineural hearing loss can

Figure 1. Unilateral dilation of ventricle on fetal ultrasound.[30]

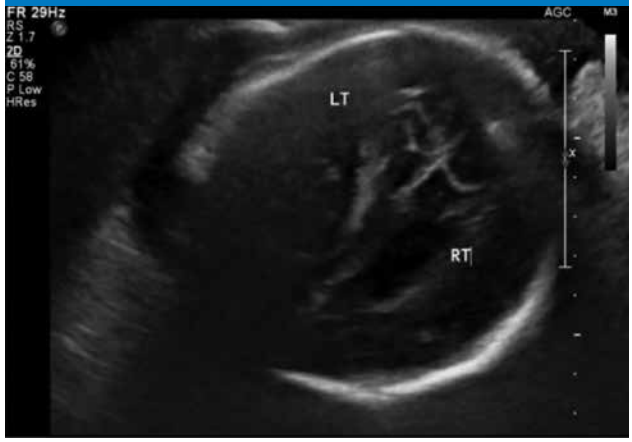


Figure 2. Chorioretinitis on fundoscopic exam.[13]

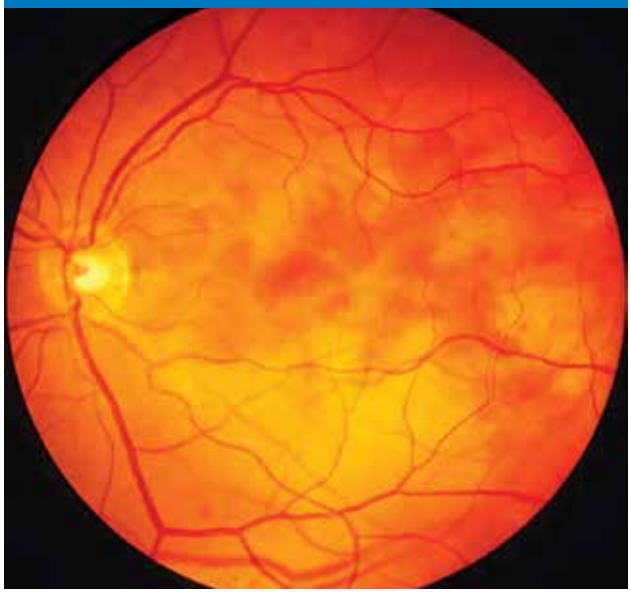
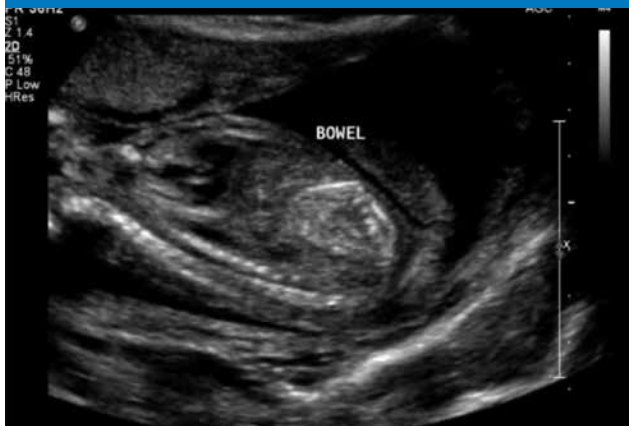


Figure 3. Hyperechoic bowel on fetal ultrasound.[30]



be unilateral or bilateral and can range in severity from mild to complete deafness.[6] Studies propose that progenitor and glial cells of the nervous system are particularly sensitive to CMV, which may be a plausible explanation for the immune-mediated damage seen throughout neural tissue in symptomatic neonates.[13]

In addition to these neurologic manifestations, infants with cCMV may also present with hepatobiliary complications. Greater than 50% of symptomatic neonates have direct hyperbilirubinemia, elevated liver function tests, and thrombocytopenia. Compromised liver function may be noticeable systemically via jaundice, petechiae, or a purpuric rash.[13]

Diagnosis/Prognosis/Prevention

Diagnosis

Concern for cCMV is often raised when abnormalities are found on fetal ultrasound in conjunction with any of the aforementioned symptoms in the mother's clinical history. While non-specific, fetal growth restriction is a common presentation found on ultrasound. Other common findings on fetal ultrasound include ventriculomegaly, microcephaly, intracranial calcifications, pleural effusions, ascites, hepatosplenomegaly, or hyperechoic bowel (Figure 3).[14] If an ultrasound scan during pregnancy shows abnormalities raising concerns for cCMV, a blood test can be done to detect maternal IgM and IgG antibodies. A positive IgG indicates a person was infected, but does not distinguish when the infection occurred. Tests that distinguish between acute infection and reactivation are based on differing avidity of the maternal IgG. The avidity is the binding strength between IgG antibodies and the virus, which is low in primary infections and matures to high strength over 2 to 4 months. A positive CMV IgM in combination with low IgG avidity is evidence for an acute, primary infection.[7]

After birth, cCMV is diagnosed via the detection of viral DNA in bodily fluids via polymerase chain reaction (PCR) of the infant such as urine, saliva, or blood within three weeks after birth. The sample must be collected less than three weeks after birth. Testing done after three weeks of life is not recommended as testing does not distinguish between congenital and postnatal infections.[7]

Prognosis

The degree of disability and early death due to cCMV varies. Neonates born with more severe symptoms typically have a worse prognosis.[15] Nearly 72% of cCMV deaths occur during the first year of life, according to a longitudinal study from 1990- 2006 by Lanzeri et al. The 557 cCMV infant deaths during the study period represented 0.11% of deaths among U.S. infants.[16]

Prevention

Strategies to reduce the burden of cCMV disease include education of pregnant women on risk-reducing behavior which leads to decreased risk of maternal primary infection, and subsequently, maternal to fetal transmission. Early detection of cCMV in newborns by universal screening is currently being evaluated through studies such as the ongoing CMV & Hearing Multicenter Screening (CHIMES) study.[17] Due to the labor and time-intensive nature of viral culture, real-time PCR assay of saliva and urine has the potential to be performed as a scalable diagnostic tool for high-volume screening. PCR of dried blood spot test for CMV testing as

part of state newborn screening has also been studied and showed promising efficacy.[18]

Other prevention methods, such as vaccination and antenatal interventions like passive immunization are also under investigation. Recent efforts with recombinant live-attenuated CMV vaccines, with deletion of genes responsible for immune evasion, have shown promise in animal models.[19]

Treatment

Antiviral Therapy

Currently, there is no universally approved treatment for cCMV. However, antiviral therapy has been utilized in some cases to mitigate the severity of symptoms and reduce the risk of long-term complications in those infected infants with central nervous system (CNS) involvement. The most commonly used antiviral drugs include ganciclovir and its oral prodrug, valganciclovir, which have demonstrated efficacy in controlling viral replication and improving hearing outcomes. These medications are typically administered to infants with symptomatic cCMV or those at high risk of developing severe neurologic manifestations.

The American Academy of Pediatrics (AAP) recommends either intravenous ganciclovir or oral valganciclovir only for infants with moderately to severely symptomatic cCMV disease who can start treatment within the first month of life. An early study performed by the Collaborative Antiviral Study Group (CASG) demonstrated that 6 weeks of intravenous ganciclovir (6mg/kg/dose given every 12 hours) improved hearing outcomes in symptomatic infants with CNS involvement. However, this study was limited by the high rate of clinically significant neutropenia that developed in patients receiving intravenous ganciclovir, as well as the challenge of maintaining long-term intravenous access. There is limited information on the effectiveness of ganciclovir or valganciclovir to treat infants with hearing loss alone.[7] Despite the AAP's recommendation, antiviral treatment in infants with cCMV without clinical findings has grown rapidly in the U.S.[20]

The decision to treat newborns with symptomatic cCMV infection must be individualized and should involve counseling regarding the potential risks like neutropenia, and benefits (improved hearing and developmental outcomes) of prolonged antiviral therapy.[19] For infants undergoing treatment with antivirals, weekly blood tests are obtained to monitor for signs of toxicity, which include complete blood count with differential, liver function tests, and kidney function tests.[21] Adverse effects with treatment include neutropenia, thrombocytopenia, hepatotoxicity, nephrotoxicity, and IV catheter complications. The use of antivirals in pregnant women with CMV for secondary prevention of cCMV have been shown to decrease the risk of transmission to the fetus, however its long term effects are still unknown. Since its safety and efficacy for the prevention of cCMV transmission during pregnancy have not been definitively established, it is not a standard practice or well established recommendation.[22]

Supportive Care and management Strategies

Supportive care plays a vital role in managing cCMV and its associated complications. This includes providing symptomatic treatment to alleviate specific symptoms such as fever, seizures, and respiratory issues. Nutritional support is essential for affected infants who may have feeding difficulties or failure to thrive. Hearing and vision interventions, such as regular screenings and early detection of sensory impairments, are crucial for prompt intervention and appropriate management. Early intervention services, including speech therapy, physical therapy, and occupational therapy, are often recommended to support the developmental needs of children affected by cCMV. Supportive measures for neonates with life-threatening disease may include fluid maintenance, transfusion of platelets and other blood products, control of seizures, oxygen supplementation and mechanical ventilation, nutritional support, and antimicrobials for secondary bacterial infection prophylaxis. The duration of prophylactic treatment is determined on a case-by-case basis.

Treatment response can be assessed by monitoring clinical symptoms of viremia with regular physical examinations, neurologic examination, hearing evaluation every three to six months, eye examination every three to six months and more frequently in those with chorioretinitis. Children with CMV also may be at increased risk of autism,[23] although this is an area of research and there are no formal screening recommendations. Appropriate referrals to neurodevelopmental services, speech therapy, occupational therapy, and physical therapy should be made on an individual basis.[24]

Immunotherapeutic Approaches

Immunotherapy is an emerging field in the management of cCMV. Passive immunization involves the administration of CMV-specific antibodies to provide immediate protection against the virus. This approach has shown some promise in reducing viral load and improving outcomes in select cases. Cytomegalovirus-specific T-cell therapy is another immunotherapeutic approach being investigated, which

involves infusing CMV-specific T cells into affected individuals to enhance the immune response against the virus. Furthermore, ongoing research is focused on developing an effective CMV vaccine, which could potentially prevent cCMV infection altogether.[25] CMV vaccines are currently in Phase II and III clinical trials.[26]

Early Screening and Diagnosis

Early screening and diagnosis of cCMV is crucial for timely intervention and management. Universal newborn screening programs have been implemented in some regions of the Canadian province of Ontario, and legislation has recently been passed for implementation in Saskatchewan and in the U.S. states of Minnesota and Connecticut.[27] Targeted newborn screening has been implemented in several U.S. states as well as other parts of the world, such as Italy's Tuscany region to detect CMV infection at birth. These programs utilize techniques such as saliva or dried blood spot testing to identify infants with cCMV (Figure 4). Early diagnosis allows for prompt initiation of antiviral therapy, if indicated, and facilitates appropriate monitoring and management of potential complications.[28] Many hospitals require newborn hearing screening prior to discharge and a referral to audiology evaluation if either ear results in a positive screening.

Psychosocial Support for Families

The impact of cCMV extends beyond the affected child and can have significant psychosocial implications for families. Providing comprehensive support and education to families is essential, as well as ensuring they have access to information, resources, and appropriate counseling. Support groups and community organizations can play a valuable role in connecting families and providing emotional support during the challenging journey of supporting a child with cCMV.

In conclusion, the treatment and management of cCMV involves a multifaceted approach that includes antiviral therapy, supportive care, immunotherapeutic approaches, early screening and diagnosis, and psychosocial support for families. Ongoing research and advancements in these areas hold promise for improving outcomes and the quality of life for infants affected by congenital CMV.[29]

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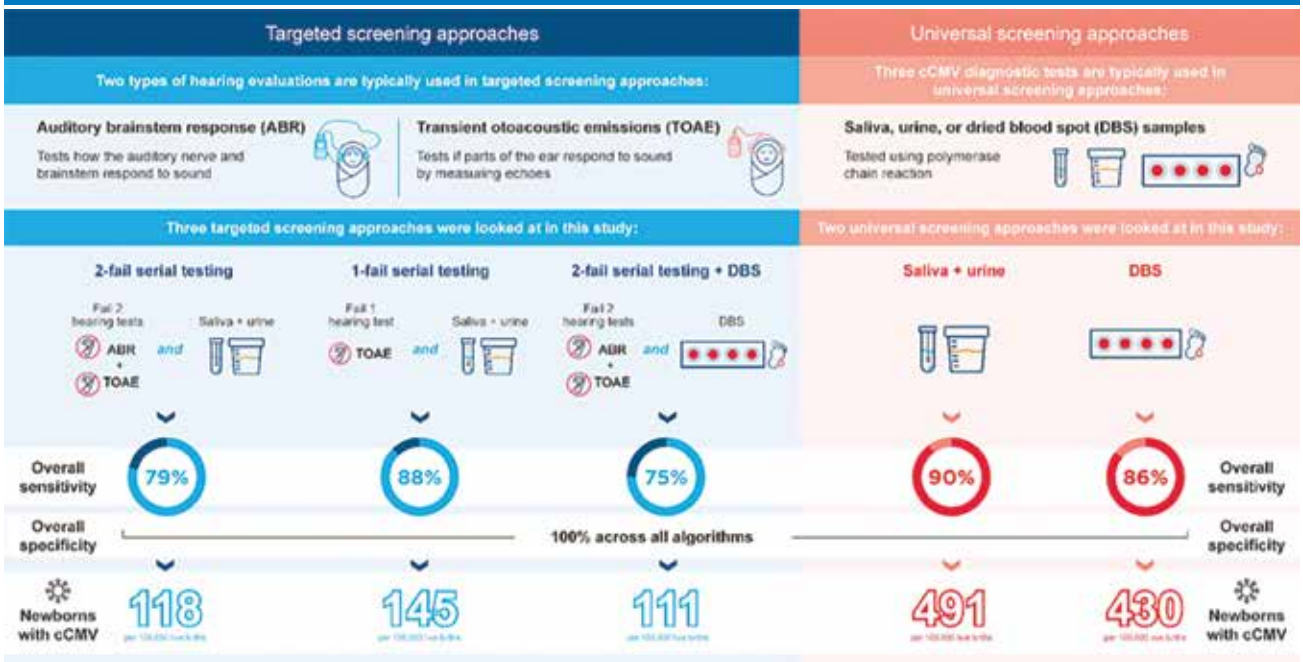
Figure 4. Screening approaches for congenital CMV.[27]



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The SDSMA works hard to ensure that you have the programs and services you want and need, as well as marketing the association to potential new members. We want to hear from you if you have questions, concerns or ideas on how we can serve you better, or if you know of a potential new member. It's your association and we'll work with you to make it the best it can be.

"For Your Benefit" is the SDSMA's monthly update on programs and services available to physicians through their affiliation with the SDSMA.

Member News

Legal Brief Highlight: Licensure

The South Dakota Board of Medical and Osteopathic Examiners (SDBMOE) has jurisdiction over the licensure and discipline of doctors of medicine and doctors of osteopathy. Except as otherwise provided by federal law, any person desiring to practice medicine or osteopathy in South Dakota must apply to SDBMOE for the appropriate license or permit. The Board is authorized by law to issue four types of licenses or permits:

1. A license to practice medicine or osteopathic medicine, surgery, and obstetrics in all of their branches without limitations – grants the privilege to practice medicine or osteopathic medicine, surgery, and obstetrics, in all their branches and without limitations. However, the license must state on its face whether it is granted to practice medicine and surgery or osteopathic medicine and surgery.

2. A temporary permit – may be granted by the SDBMOE if it appears that an urgent need exists in any state-owned and operated medical institute for the services of a practitioner of medicine, surgery, and obstetrics and their branches.

3. A locum tenens certificate – allows the practice of medicine in South Dakota for a time period not exceeding 60 days to an applicant who is a current holder of a valid license to practice medicine or osteopathy in any state or territory of the U.S., the District of Columbia, or province of Canada, or who has graduated and received a diploma from an approved medical or osteopathic college and who has completed at least one year of an approved internship or residency program or its equivalent.

4. A resident certificate – issued to an applicant currently enrolled in an accredited residency program. A resident certificate is valid for one year from the issue date.

For more information, access the SDSMA legal brief Licensure at sdsma.org. The SDSMA provides legal briefs for member physicians on a variety of rules and regulations that apply to the medical profession. For nonmembers, legal briefs are available for purchase.

COPIC Tips: 5 Systems for Follow-up Tracking

COPIC, the SDSMA's endorsed carrier, has provided information to encourage practices to implement systems for tracking and managing patients and events requiring follow up. Failure to follow up by one or more parties is a recurrent cause of preventable errors. Because of the importance of these systems to patient safety, the following are five areas of high concern:

Patient follow up – This involves "closing the loop" by notifying patients when they need a subsequent visit, or by contacting and notifying providers if a patient fails to follow up when needed. Non-adherence with recommendations may have risks serious enough to require a distinct "informed refusal" process. More often it is sufficient to document instances such as missed appointments, failure to take medications as recommended, failure to follow medical advice, failure to schedule a recommended test or procedure, or failure to see a consultant when advised.

Consultations and referrals – This focuses on a system to alert the referring provider that a previously arranged consultation did not occur, for example with another provider or facility. It includes systems for communicating in both directions between primary care and specialty consultants—and between specialists—when the patient's non-compliance may have significant clinical consequences.

Test results – This involves a system to review and act on on-site and off-site laboratory tests, imaging, pathology, and other diagnostic procedures that generate results needing review and potentially further action.

Received reports and correspondence that require review – This involves a system to process and act on information received from external sources. This information may not necessarily have been initiated by the treating provider.

Patient notification of test results and recommendations – This involves a system to communicate results, information and recommendations to patients who are not physically present.

Whether done manually (e.g., a card file) or with computer-assistance, systematically managing these five areas can be accomplished with a dedicated workflow for each, or through one comprehensive, follow-up and tracking system.

In its most basic form, a follow-up system is a "tickler file." Electronic applications for this purpose can offer significant advantages. However, they need careful configuration and testing. Although most EHRs offer reminder and alert functions in various forms, COPIC's experience is that many of these may have serious flaws and gaps that inevitably require human intervention. This implies that both providers and support staff have important roles in the system. Furthermore, involving patients in the workflow for monitoring future agenda items (especially if these become overdue) adds a valuable layer of safety.

Save the Date! 2024 SDSMA Annual Leadership Conference

Join us for a day of learning and engagement at the 2024 SDSMA Annual Leadership Conference on Friday, May 31 at the Holiday Inn Rapid City Downtown as we address Native American healthcare issues.

Native American communities face a complex set of issues and concerns regarding healthcare, resulting in significant disparities compared to the general population. Attend the conference to gain valuable insights and contribute to advancing healthcare for Native American patients in South Dakota.

Additionally, network with colleagues and attend the poster session where USD Sanford School of Medicine students will highlight their work.

Check sdsma.org for more details, sponsorship opportunities, and attendee registration soon.

Don't forget to send in your favorite scenic photo for

South Dakota Medicine

front cover consideration.

Send photos to ereiss@sdsma.org.

SOUTH DAKOTA
BOARD OF MEDICAL & OSTEOPATHIC EXAMINERS

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- Licenses and regulates over 11,500 licenses within fourteen different medical categories
- Establishes regulations by proposing legislation and adopting administrative rules
- Provides Safe Haven, supports, and promotes confidential monitoring of its healthcare providers

Board News is a monthly feature sponsored by the South Dakota Board of Medical and Osteopathic Examiners. For more information, contact the Board at SDBMOE@state.sd.us or write to SDBMOE, 101 N. Main Avenue, Suite 301, Sioux Falls, SD 57104.

BEYOND COVERAGE

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COPIC is proud to be the endorsed carrier of the South Dakota State Medical Association. SDSMA members may be eligible for a 10% premium discount.

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Help Shape the Future of Medicine in South Dakota

The South Dakota State Medical Association Foundation, the philanthropic arm of the South Dakota State Medical Association, is a tax-exempt 501(C)(3) non-profit corporation, was established to assist and support medical research, medical teaching and medical education at the Sanford School of Medicine.

On average, medical students graduate with $130,000 in debt. Contributions to the South Dakota State Medical Association Foundation provide financial assistance to students at the Sanford School of Medicine and are all designated for scholarships, grants and low-interest loans for students.

Any amount can be donated at any time throughout the year. If you have questions or want more information, please call 605.336.1965.

Send Your Contributions Today To:
South Dakota State Medical Association Foundation
2600 W 49th St Ste 100, Sioux Falls, SD 57105
Or contribute online at www.sdsma.org

SOUTH DAKOTA
State Medical Association Foundation
Shaping the Future of Medicine in South Dakota