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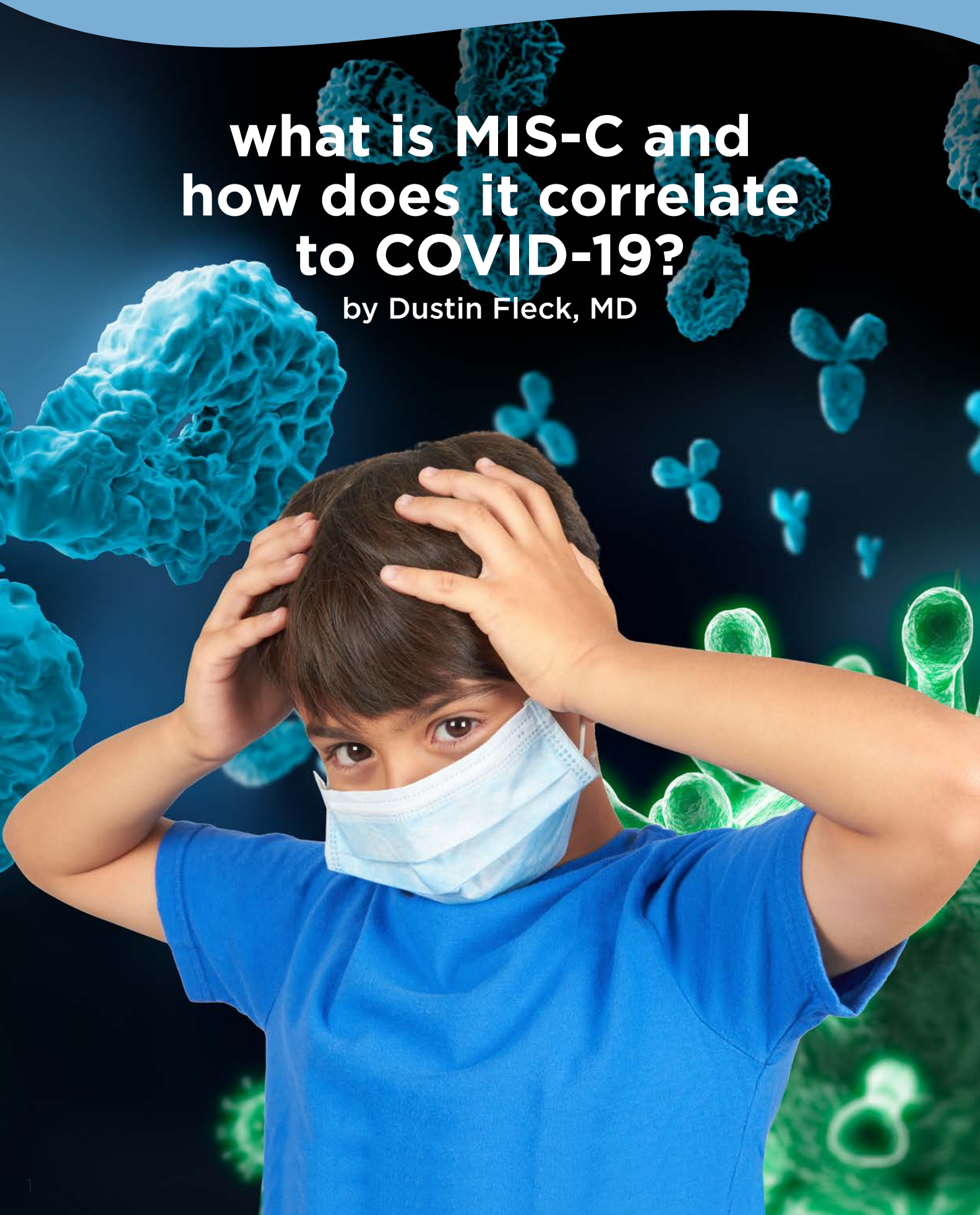

what is MIS-C and how does it correlate to COVID-19?

by Dustin Fleck, MD

learning objectives

Following the completion of this article, the reader should be able to:

1. Understand the clinical features and diagnostic criteria for MIS-C.
2. Recognize the various presentations and complications including macrophage activation syndrome (MAS).
3. Learn various pharmacotherapeutic interventions for treatment of MIS-C.

The novel coronavirus SARS-Cov-2 (also known as COVID-19) has created multiple challenges to the medical community ranging from patient access and overburdened hospital units to decreased preventative care. With this novel virus has come a new inflammatory post-infectious entity. In the world of rheumatology, we are no strangers to post-infectious inflammatory disorders. Our disease repertoire consists of the likes of rheumatic fever, post-infectious transient synovitis, macrophage activation syndrome and Kawasaki (with some belief that this is a viral/post-viral process due to its seasonal variation). Over the decades, scientific advances have led to the discovery of pre-existing unknown autoimmune processes such as anti-NMDA receptor encephalitis, but never have we been faced with such an unforeseen development of a new inflammatory malady.

Faced with a surge of SARS-Cov-2 infections in Spring 2020, France began implementing school closures and lockdowns on March 17 to face the outbreak. Weeks later, the Necker Hospital for Sick Children's general pediatric service began to see a disproportionate number of patients admitted with a Kawasaki-like disease and myocarditis, with over 20 patients admitted from April 27 to May 11, 2020.[1] Initially referred to as pediatric inflammatory multisystem syndrome (PIMS), this entity came to be known as and is now termed multi-system inflammatory syndrome in children (MIS-C).

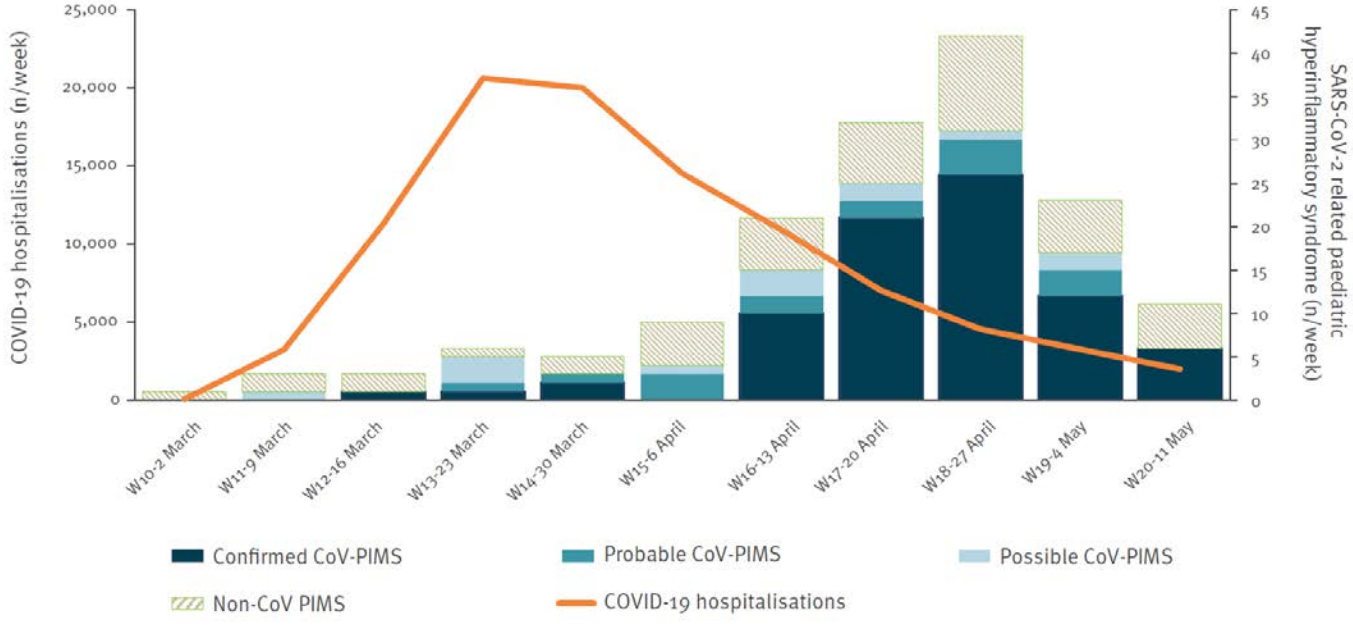

figure 1. Temporal distribution of COVID-19 hospitalizations and SARS-CoV2 hyperinflammatory pediatric cases, France, 2 March-17 May (n=108)

what is MIS-C?

MIS-C is a hyperinflammatory syndrome that occurs in children likely in response to recent COVID-19 infection. It is not generally associated with active viral infection, but instead has a temporal correlation with COVID-19, occurring generally 2-4 weeks after infection. Children with symptomatic or asymptomatic COVID-19 infections may go on to develop this hyperinflammatory response. MIS-C can have varying presentations and mimic other conditions such as Kawasaki disease, toxic shock syndrome or macrophage activation syndrome with some potential overlap in its various presentations. It is characterized by fever, systemic inflammation and multi-organ involvement. The pathogenesis of MIS-C is still under investigation and its direct link to COVID-19 is currently a likely hypothesis, but not yet proven.

diagnosing MIS-C

The following diagnostic criteria for MIS-C has been issued by the Centers for Disease Control and Prevention (CDC)[2].

Patient under the age of 21 presenting with:

- Fever (>38.0°F objectively measured, or subjective fever for at least 24 hours)
- Laboratory evidence of inflammation
  - Including but not limited to elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, fibrinogen, procalcitonin, d-dimer, lactic acid dehydrogenase (LDH)
- Clinical illness of severity warranting hospitalization
- Multisystem involvement with two or more organs involved:
  - Gastrointestinal (most common)
  - Dermatological
  - Cardiac
  - Hematologic
  - Neurologic
  - Renal
  - Respiratory
- Current or recent COVID-19 infection confirmed by:
  - SARS-CoV-2 infection by PCR
  - SARS-CoV-2 positive serology
  - Exposure or suspected symptoms within 4 weeks of presentation
- No alternative plausible diagnosis

diagnostic criteria for Kawasaki disease
1. Fever for 5 days or longer
2. Presence of 4 out of 5 of the following:
- Changes in extremities: Erythema/edema
- Polymorphous exanthema (rash)
- Bilateral and painless conjunctival injection
- Mucosal findings: Lip cracking/strawberry tongue
- Cervical lymphadenopathy (>1.5cm)

table 1. Diagnostic criteria for Kawasaki disease

disease characteristic	Kawasaki	MIS-C
High risk	Asian	African
Incomplete form	5-20%	48%
GI symptoms	Not common	100%
Shock syndrome	2-7%	57%
Myocarditis/Ventricular dysfunction	<1%	76%
ICU care required	4%	81%
Coronary artery findings	4-13%	24%
IVIG resistance	10-20%	24%

table 2. Comparison of Kawasaki disease versus MIS-C

MIS-C presentation

Age range for patients is broad, but case series show the typical presentation occurring between the ages of 5 to 11 with an equal 1:1 male to female propensity. The severity of MIS-C varies, but more than two-thirds of patients warrant ICU level care. Nearly 100% of patients have some element of gastrointestinal involvement and 70% have some level of myocarditis. The most typical symptoms include fever (100%), abdominal pain/diarrhea (73.7%), emesis (68.3%), rash (56.2%), conjunctivitis (51.8%), cheilitis (32.6%), headache/dizziness (19.5%), extremity edema (19.3%), dyspnea/shortness of breath (18.3%), lymphadenopathy (13.9%), myalgia (13.4)%, cough (13%), loss of appetite (11%), lethargy (10%), sore throat (8.9%), rhinorrhea/congestion (7.1%), and tongue swelling (4.7%).[3] Most patients have symptoms/presentations that closely mirror the more well known and defined Kawasaki disease. The criteria for Kawasaki is shown in Table 1.[4]

Table 2 compares some characteristic differences between MIS-C and classic Kawasaki disease.[5] Up to one-

quarter of patients may present with an element of macrophage activation syndrome (MAS), a syndrome most often seen in conjunction with rheumatic disorders such as systemic onset juvenile idiopathic arthritis (SoJIA). MAS is characterized by expansion and excessive activation of T lymphocytes and macrophagic histocytes with hemophagocytic properties. These cells can subsequently infiltrate various organs such as the liver, spleen and bone marrow with subsequent coagulopathies, liver dysfunction, and cytopenias. Standard hemophagocytic lymphohistiocytosis (HLH) diagnostic criteria are often used for MAS, for which five out the eight following criteria must be met for diagnosis:

1. Persistent fever
2. Splenomegaly
3. Cytopenias (two or more lineages affected)
4. Hypertriglyceridemia (>265mg/dl) or hypofibrinogenemia (<1.5g/L)
5. Hemophagocytosis in bone marrow, spleen or lymph nodes
6. Serum ferritin (> 500mg/L)
7. Low or absent NK cell activity
8. Increased serum SIL2R alpha

Untreated, MAS carries a 20-30% mortality risk.[6] Patients presenting with MIS-C with MAS-type features often require more aggressive therapies with IL-1 inhibitors.

outcomes

Many concerns regarding MIS-C revolve around short-term and long-term outcomes. The most comprehensive systematic review to date (581 MIS-C patients) shows that cardiac manifestations are of the most concerning. Over half of patients with MIS-C have abnormal echocardiograms with findings of depressed ejection fraction (45.1%), depressed shortening fraction (36.4%), pericardial effusion (22%), and aneurysm (8.1%). Both demonstrated in the literature as well as via clinical experience here at Dayton Children's, initial echocardiograms are often normal, only demonstrating abnormalities days into their hospital admission. One-third of patients had EKG abnormalities, mean troponin levels were 494ng/L (Normal <10ng/L), and mean brain natriuretic peptide (BNP) levels of 3604pg/mL (normal 0-100pg/mL). Mechanical ventilation was required in 22.2% and extracorporeal membrane oxygenation (ECMO) required in around 4% of patients. The average length of hospitalization for MIS-C is approximately 8 days.[3] The mortality rate of MIS-C is low at 1.7% with 11 patients reported in the literature. However, this is significantly higher than the 0.01% mortality rate seen in Kawasaki's disease.[7]

treatments

Given the novelty of COVID-19 and its inflammatory sequalae, there has been no clinically proven therapies for MIS-C, but many agents have been demonstrated to be effective based on clinical review and experience. MIS-C is likely self-limiting; a few select mild cases may be observed with supportive care and close monitoring for progressive cardiac manifestations. The most widely used agent for MIS-C is intravenous immune globulin (IVIG), which is a pooled collection of antibodies from between 1,000-15,000 donors.

IVIG's mechanism of action in most autoimmune/autoinflammatory disease is likely related to activated T cell inactivation via competitor mechanism with antigen presenting cells. Studies have shown

that there is restoration of balance in inflammatory cytokines. This is postulated to work via multiple mechanisms, but ultimately leads to down regulation of an excited immune system, while not being immunosuppressive.[8] Its effectiveness in MIS-C is likely related to its overlap with Kawasaki, and it is believed that IVIG may help prevent cardiac complications and coronary aneurysms in MIS-C. Over 75% of patients presenting with MIS-C ultimately get treated with IVIG therapy, making it the top agent, surpassing even corticosteroids (52.3%).

Although IVIG is often rapidly effective, many patients with MIS-C require a second dose of therapy and in select few cases, escalation to biologic therapy. Corticosteroids have been used in a wide variety of forms, including high intravenous dosing (pulse dose), frequent smaller IV dosing, oral dosing, and prolonged tapers based on patient severity and duration of symptoms. A variety of different corticosteroids have been used, including methylprednisolone, prednisone dexamethasone and hydrocortisone.[9]

Patients who fail typical first line therapy with IVIG, present with severe hemodynamic instability, or develop features of macrophage activation syndrome may benefit from biologic agents such as anakinra, an IL-1 inhibitor. These agents have been found to possibly be helpful also in adults with active COVID-19 who develop cytokine storm syndrome. Tocilizumab is the agent most associated with this, an IL-6 inhibitor that gained more traction due to the lack of availability of anakinra in the regions hit earlier in the pandemic. It is also well known for its use in cytokine storm syndromes associated with malignancies. Anakinra was first approved in 2001 and is used in many autoinflammatory conditions such as macrophage activation syndrome, hereditary periodic fever syndromes (familial Mediterranean fever, mevalonate kinase deficiency, cryopyrin associated periodic fever syndromes to name a few), systemic onset juvenile idiopathic arthritis, recurrent idiopathic pericarditis and more. Its onset of action is swift due to its peak within 3 hours but requires frequent dosing (once daily) due to its 4-6-hour half-life. Unless contraindications are present such as thrombocytopenia, low dose aspirin therapy (3-5mg/kg/day; max 81mg/day) is generally recommended and continued until both platelet counts normalize to less than 450,000 and there is confirmation of no coronary artery abnormalities one month after diagnosis. Escalation to enoxaparin may be warranted in patients with an ejection fraction <35%, coronary artery aneurysms with a Z score >10.0, or evidence of thrombosis or persistent moderate to severe left ventricular dysfunction.[10]

long-term outcomes

Of concern for MIS-C going forward is potential long-term sequelae or risk of reoccurrence. Many of our post-infectious or other transient inflammatory syndromes come with a plethora of scientific studies and long-term observational studies. Kawasaki disease was first described in 1967, while rheumatic fever was described in 1889. MIS-C having only been recognized in April 2020 comes with an ever-growing collection of case series and short-term studies, but it will take time to learn the long-term implications of MIS-C.

conclusion

Children with MIS-C present with fever, laboratory evidence of inflammation with multisystem involvement, often with gastrointestinal involvement, and run a high risk of cardiac involvement. It is temporarily related to COVID-19 infections, generally occurring 2-4 weeks after. It can be mild and treated with supportive care, but often requires ICU level care and treatment with IVIG, corticosteroids or less commonly, IL-inhibitor therapy. Given its presentation, it is imperative that other plausible diagnoses such as infectious, oncologic or rheumatologic etiologies are not present.

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CME questions

1. **Which organ system has the highest frequency of involvement in patients with MIS-C?**
   - **a. Cardiac**
   - **b. Respiratory**
   - **c. Gastrointestinal**
   - **d. Neurologic**
2. **Intravenous immunoglobin therapy is the most commonly used therapy for patients with MIS-C**
   - **a. True**
   - **b. False**

sepsis in children

by Merrilee Cox, MD

case vignette

A teenage patient with IBD was admitted for bowel surgery. She did well the first two days following surgery, and the plan was to discharge her home on post-op day 3. On the morning of post-op day 3, the patient's heart rate increased to 112, followed shortly afterwards by a temperature of 38.6°C. She was initially given acetaminophen, which improved her fever; however, her heart rate continued to climb into the 130s. Ten hours after her symptoms began, the patient was given her first fluid bolus without significant improvement in her symptoms. The patient received another bolus during the next 12-14 hours, again without improvement. By the following morning, the patient was noted to have evidence of multi-organ system failure and was transferred to the ICU.

learning objectives

Following the completion of this article, the reader should be able to:

1. Explain the current definition of pediatric sepsis and the challenges with recognizing pediatric sepsis.
2. Summarize key recommendations on the recognition and management of pediatric sepsis.
3. Describe processes implemented at Dayton Children's to improve the rapid recognition and management of pediatric sepsis.

the problem

Sepsis is a significant cause of pediatric morbidity and mortality worldwide. In 2017, nearly half of global sepsis cases occurred in children aged 5 and under, and in 2018, 15% of neonatal deaths were attributed to sepsis.[1]

According to the Sepsis, Prevalence, Outcomes and Therapies Study, the overall prevalence of pediatric sepsis in the 26 participating countries was 8.2%, with a 25% mortality rate. Within the U.S., one-third of children who die within pediatric ICUs have evidence of

sepsis. From a morbidity standpoint, 67% of children with sepsis had multi-organ system failure at the time of diagnosis, and 17% of survivors had long-term disability.[2] The national estimated cost of pediatric sepsis in 2016 was $7.31 billion, which was a 25% increase in inflation-adjusted costs since 2005.[3] Recently, the World Health Organization (WHO) identified sepsis prevention, identification and early management as priorities for the upcoming decade.[1]

Defining sepsis has been an ongoing challenge. The adult sepsis definition has undergone several updates since the early 90s, with the most recent definition published in 2016. The Sepsis-3 definition states that sepsis is life-threatening organ dysfunction caused by dysregulated host response to infection. Moving away from the systemic inflammatory response syndrome (SIRS) as the foundation of sepsis, the updated definition focuses on organ dysfunction, as demonstrated by a change in the systemic organ failure assessment (SOFA) score of 2 or more. Originally designed for research purposes, the current pediatric definition has not undergone any changes since its establishment in 2005, and still requires a patient to meet criteria for SIRS and have a presumed or confirmed infection.[4] Severe sepsis includes at least dysfunction in one organ system, and septic shock further includes acute circulatory failure as demonstrated by persistent hypotension. Unfortunately, many conditions in pediatrics create an inflammatory response, leading to under-recognition of patients who are developing sepsis, often reinforced by diagnosis momentum and anchoring biases.

Sepsis can result from infections caused by bacteria, viruses, fungi and parasites, which cause the release of inflammatory mediators and induction of intracellular dysfunction. The most common bacterial agents include Escherichia coli, Staphylococcus aureus, coagulase-negative Staphylococcus, and Streptococcus pneumoniae. However, only half of pediatric ICU patients with sepsis have a proven microbiologic infection.[5] Three mechanisms contribute to the development of sepsis. The first is an excessive pro-inflammatory response, mediated by TNF-α, IL-1 and IL-6. The second is a failure of the compensatory anti-inflammatory response leading to overall imbalance and uncontrolled inflammation. The third is the development of an acquired immunodeficiency due to the overwhelming of the immune system by the inflammatory mediators.[6] Recent genomic research has identified three inflammatory genotypes that are associated with increased rates of macrophage activation syndrome and mortality in children with sepsis with multi-organ failure.[7]

Early recognition of sepsis is challenged by the physiologic differences of children as compared to adults, as well as the normal variation in vital signs related to age. For example, a normal heart rate for an infant can vary between 95 to 180 beats per minute, while a 12-year-old's heart rate ranges from 50 to 120.[8] The signs and symptoms of pediatric sepsis are also more subtle than in adults, making recognition difficult, especially for residents rotating from adult-based programs.[9] Weiss et al. found mortality and organ dysfunction increased when there was a 3-hour delay in antibiotic administration.[10]

The Surviving Sepsis Campaign published pediatric-focused guidelines in February 2020. The guidelines focus on sepsis with end-organ dysfunction and septic shock, which is more in line with the Sepsis-3 adult criteria. Early recognition utilizing automated warning systems, rapid instillation of crystalloid fluids, and prompt initiation of broad-spectrum antibiotics followed by appropriate antibiotic stewardship make up some of the key recommendations for care applicable outside of the critical care environment. Additionally, the guidelines encourage the development of standardized protocols to aid in the timely response and management.[11] The American College of Critical Care Medicine (ACCM) proposed bundled approaches to managing sepsis including recognition, resuscitation, stabilization and performance bundles.[12]

implementing a sepsis bundle

We recognized the imperative to develop an inpatient sepsis bundle to improve our approach to patients who develop sepsis while admitted to Dayton Children's. Through the Ohio region of Solutions for Patient Safety, Dayton Children's implemented a situation awareness bundle in 2014. The goal of the situation awareness bundle is to identify patients who are at risk for medical deterioration or adverse events, develop robust mitigation plans, and to escalate care as needed. Given the similarity to the

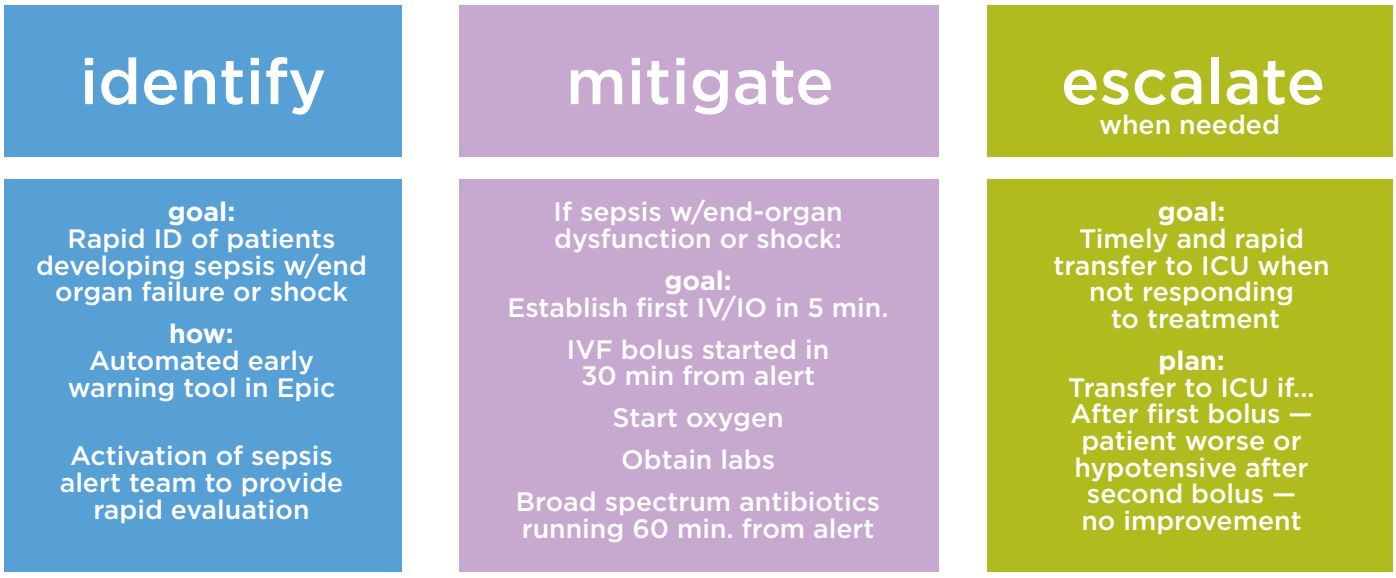

figure 1. Sepsis bundle for Dayton Children's. The bundle includes the three bundle elements of situation awareness, including identification, mitigation, and escalation when appropriate. IV = peripheral IV, IO = intraosseous line, IVF = intravenous fluids, ICU = intensive care unit.

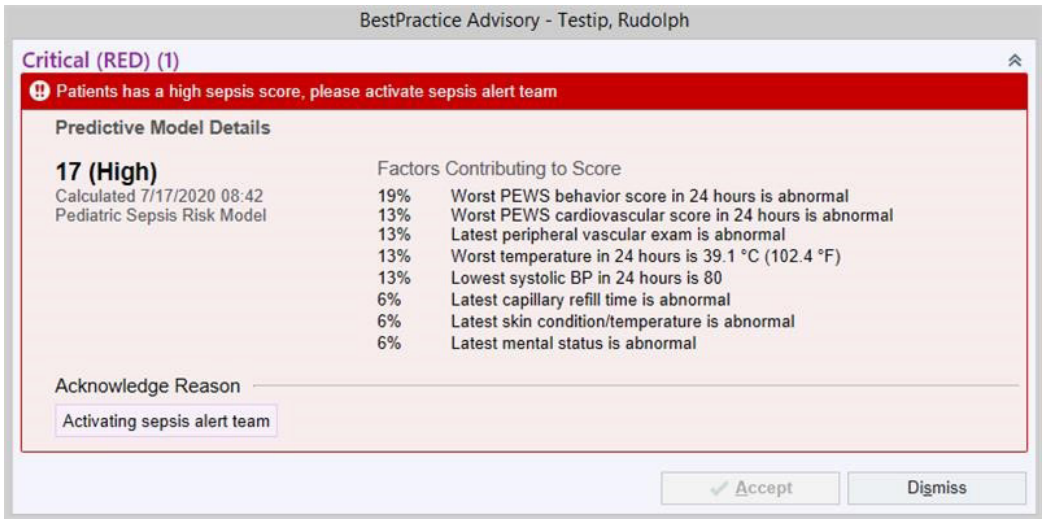

figure 2. Example of best practice alert for sepsis scoring system. Health care team members are able to view what components contributed to the score exceeding the threshold.

recommend bundle approach by the ACCM, we felt that our bundle should be built utilizing the situation awareness framework (figure 1).

identification

Recognizing the challenges with early identification of sepsis, we sought to utilize the electronic health record (EHR) to aid with early detection. EHRs can review patients' charts on a regular interval and apply scoring algorithms to determine a risk level for sepsis. According to Amland et al., ideal sepsis clinical decision support tools need to be patient-centric, at the point of care, and provide real time data to the end-users.[13] Our EHR system, Epic, had recently developed a pediatric specific algorithm designed for use in the emergency department and the non-critical care inpatient areas, excluding hematology-oncology. The scoring system reviews each patient chart every 15 minutes, utilizing vital signs, clinical assessments, lab work, and the presence of high-risk conditions in its calculation of the sepsis risk score. In the inpatient arena, if a threshold of 11 or higher is met, a best practice alert fires letting the health care team know that the patient is at high risk for sepsis (figure 2). While this is a screening system and a degree of false positives is expected, trying to balance the sensitivity with the specificity is crucial to help reduce alert fatigue.

To assure rapid evaluation of patients with potential sepsis, we developed a rapid response team specific for sepsis through a series of plan-do-study-act cycles. Multiple health care facilities have created diagnosis-specific rapid response teams, such as the stroke teams commonly seen in adult facilities. The sepsis team consists of a pediatric hospitalist, the admitting resident of the day, the bedside nurse, a phlebotomist and a

respiratory therapist. Once the best practice alert fires, a team member, usually the bedside nurse, activates the team through our hands-free communication device. Available 24 hours a day, the team responds to calls for patients on our non-critical care inpatient units, except hematology-oncology. The team is expected to be at the bedside within 10 minutes of the alert, rapidly assess the patient and determine if the patient is meeting criteria for sepsis with end-organ failure or septic shock, and begin interventions. Since the providers may be responding to a patient for whom they do not have primary responsibility, they are expected to contact the attending of record to make them aware of the situation, and obtain any additional necessary information about the patient, which may help guide further interventions.

mitigation

According to the Surviving Sepsis guidelines, rapid intervention is key to reducing morbidity and mortality.[11] Sepsis with end-organ failure and septic shock require rapid fluid resuscitation to improve cardiac output and end organ perfusion. Vascular access must be established quickly, and every effort should be made to eliminate delays in obtaining access in those who do not already have an IV. First vascular access should be established by 5 minutes from the time of the team's arrival. Immediate access to IV supplies or an intraosseous drill is crucial; therefore, the nurse brings these supplies, as well as lactated ringers to the bedside while the team is assembling. A 20ml/kg bolus of crystalloid fluids given over 30 minutes (faster if the patient is in shock) and before 30 minutes post-alert is the next priority. Lactated ringers replaces normal saline as the preferred resuscitation fluid due to concerns of hyperchloremia and worsening metabolic acidosis, which has been associated with worsening morbidity.[11]

Recommended laboratory evaluation includes a complete blood count, comprehensive metabolic panel, procalcitonin, lactic acid and blood culture. These provide information regarding the level of system involvement. Ideally blood cultures should be obtained prior to the administration of broad-spectrum antibiotics; however, if this will lead to a significant delay, the antibiotics should be prioritized. Procalcitonin has been shown in multiple studies to be a useful marker in the prediction of sepsis, both in adults and children.[14,15] Additional laboratory testing and imaging should be completed based on the history and clinical exam of the patient.

The last focus of the initial mitigation is the initiation of broad-spectrum antibiotics. The Surviving Sepsis guidelines note that for patients with septic shock antibiotics should be initiated within the first 60 minutes, and for those with sepsis with end-organ dysfunction as soon as possible but no later than the first three hours.[11] Since patients who develop sepsis in the inpatient area may already be on antibiotics, a quick review of what they have received, and consideration of the likely etiology and potential need for broadened coverage must be completed. To assist responding teams, we created a standardized order set with recommended antibiotic choices, which populate based on the age of the patient. Ceftriaxone and vancomycin are the mainstays of therapy for patients over the age of two months. Metronidazole is added when there is concern for an intra-abdominal process. In the past, piperacillin-tazobactam has been a drug of choice for intra-abdominal infections, but, especially when given in combination with vancomycin, has been implicated in many cases of nephrotoxic acute kidney injury. Improving multidisciplinary situation awareness, the on-call pharmacist also receives the alert so he or she can be ready for STAT antibiotic orders.

escalation

The hallmark of a robust mitigation plan is the prediction of outcomes based on the therapies provided and the next steps if those outcomes are not met. For sepsis with end-organ dysfunction and septic shock, the goal of the interventions is to reverse the deterioration and improve the risk of morbidity and mortality. Frequent reassessments of the patient after each fluid intervention are critical for three reasons. First, the patient's cardiac output must be evaluated through the assessment of perfusion and vital signs. If the patient is still showing signs of impaired cardiac output, e.g. delayed capillary refill, hypotension or a depressed mean arterial pressure (MAP), or tachycardia, then a repeat bolus should be given. Second, the patient

must be assessed for signs of fluid overload, as evidenced by the presence of rales, edema, a change in mental status or hepatomegaly. If there are signs of fluid overload, further boluses are not recommended. Third, once the patient has received 40-60ml/kg or has fluid overload and continues to have impaired perfusion, prompt initiation of vasopressor medications is recommended. These should be initiated in an intensive care setting to allow for the appropriate monitoring required. Once a patient has demonstrated they need critical care interventions, the team contacts the on-call ICU physician to accept the transfer of the patient. To facilitate the transfer, both the charge nurse in the intensive care unit and the clinical logistics nurse receive the sepsis alert, allowing them to identify a potential ICU bed.

conclusion

We developed a standardized bundled approach to non-critical care inpatients developing sepsis to improve early detection and rapid intervention, with the goal of reducing the incidence of multi-organ system failure and mortality associated with sepsis. Use of an automated warning tool within the EHR improves our ability to detect developing sepsis at earlier stages than what was traditionally seen when relying on clinical judgment alone. While we initially tested the bundled approach with patients admitted to hospital medicine, we have since spread to other services, such as pediatric surgery and orthopedics. In the future, we would like to evaluate the application of the sepsis bundle to our hematology-oncology department, although we recognize we will likely need to make some adaptations based on the additional needs of that patient population.

Additionally, we continue to investigate whether the EHR can send the alert directly to the hands-free communication device, thereby eliminating a potential delay in the process.

Sepsis continues to remain a significant issue throughout the world. Prevention, early recognition and prompt management are the keys to reducing sepsis-related morbidity and mortality.

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Merrilee Cox, MD

Merrilee Cox, MD, is the chief medical safety officer for Dayton Children's, a board-certified pediatric hospitalist and an assistant professor in pediatrics. She trained at Wright State University School of Medicine, completing her general pediatric residency at Dayton Children's with the United States Air Force. Dr. Cox joined the hospitalists in 2007 while also serving as the Director of Medical Education. Driven by a growing passion to improve the safety of the care we provide, she transitioned to the chief medical safety officer in 2013. She graduated in 2020 from Johns Hopkins University Bloomberg School of Public Health with a Master of Applied Science in patient safety and healthcare quality. She is currently serving a three-year term as one of the Ohio Region Champions for Solutions for Patient Safety.

CME questions

3. **Early recognition of sepsis in pediatrics is challenging due to the subtleties of presenting signs and symptoms.**
   - **a. True**
   - **b. False**
4. **Using a protocolized approach to sepsis can help reduce morbidity and mortality.**
   - **a. True**
   - **b. False**
5. **Blood cultures should always be prioritized over giving antibiotics in patients with sepsis.**
   - **a. True**
   - **b. False**

advancing technologies for treatment of type 1 diabetes in children

by Yelena Nicholson, DO

In 2018 the American Diabetes Association (ADA) and Centers for Disease Control and Prevention (CDC) estimated that 34.2 million Americans or 10.5% of the population had diabetes. Nearly 1.6 million Americans have type 1 diabetes, among them 187,000 children and adolescents.[1] The incidence of diabetes in youth younger than 20 years increased in the U.S. between 2002 and 2015 with 4.8% increase per year for type 2 diabetes and 1.9% increase per year for type 1 diabetes.[2] The treatment and quality of life of patients with insulin dependent diabetes, especially children, have changed and continues to change dramatically.

learning objectives

Following the completion of this article, the reader should be able to:

1. Review technological advances in the management of type 1 diabetes.
2. Describe advances in the treatment of type 1 diabetes and the impact on glycemic control and the quality of life of patients and families.
3. Discuss the need for new technologies in diabetes management.

Let's briefly look at the history of insulin dependent diabetes management in the past:

- Ancient Hindu writings (approximately 1500 BC) mentioned description of mysterious diseases with symptoms of diabetes. The words *diabetes mellitus* are derived from Greek and Latin words meaning "to pass through sweet or honeyed," which refers to the excess sugar found in the blood and urine of diabetic individuals.
- Treatment of type 1 diabetes in the 17th century involved either ingestion of excessive sugar to replace that lost in urine or restriction of dietary sugar.
- In 1869 German medical student Paul Langerhans discovered that islet cells of the pancreas produce insulin.

- The average life expectancy for a 10-year-old child with type 1 diabetes in 1897 was 1.3 years.
- In 1920 Drs. Banting and Best used insulin (pancreatic extract) to lower sugar in dogs with removed pancreases.
- In 1922 Leonard Thompson, a 14-year-old boy from Toronto, became the first person to receive insulin injections. (Figure 1)
- In 1923 Eli Lilly becomes the first pharmaceutical company to commercially produce insulin.
- Short, intermediate and long-acting insulins became available in the 1950s.
- Through the 1950s and 1960s home monitoring kits were used to detect the level of glucose in urine.
- In the 1970s evolving technology brought home glucose monitoring, revolutionizing diabetes care with the ability to do multiple blood sugar tests a day at home.
- The 1970s also brought the first insulin pump (utilizing a microwave oven-sized backpack that continuously dispensed insulin).

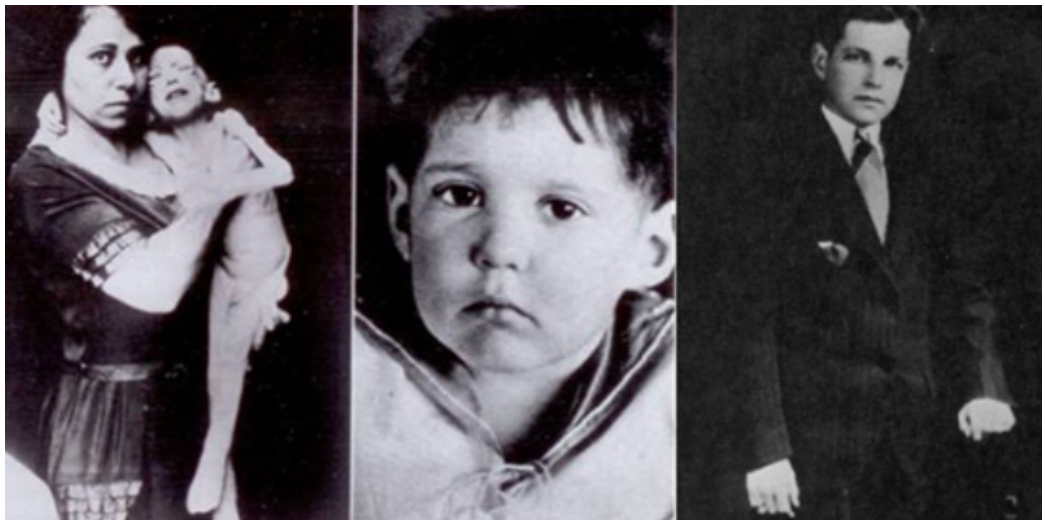

figure 1. Leonard Thompson, the first patient to receive insulin injections. He is pictured at age 14 years with his mother, within six months of insulin injections, and at age 27 years.

- The 1980s witnessed the evolution of personal insulin pump therapies using a continuous subcutaneous insulin infusion (CSII) approach that became an alternative to multiple daily injection insulin therapy (the standard of insulin dependent diabetes care in 80s and 90s).
- In 1996 the U.S. Food and Drug Administration approved the first biosynthetic insulin, Humalog. These newer insulins became known as analog insulins.
- With the 2000s, widespread use of insulin pump therapies and a variety of different insulin pumps were developed and implemented in the care of patients.
- In the 2010s continuing glucose monitoring systems (CGMS) were able to follow blood sugar levels continuously and in many cases replaced finger stick glucose monitoring.

Current technology is focusing on looping insulin delivery/glucose monitoring where both a pump and CGMS work jointly in developed algorithms to maintain blood glucose levels within a normoglycemic range similar to the range of blood glucose levels in persons without insulin dependent diabetes.

Technological advances in diabetes treatment have made it possible to improve diabetes control and lower HgA1C in patients without increasing the work on the part of the patient or parents. Achieving euglycemia and reducing hemoglobin A1C (HgA1C) levels are important to prevent morbidity and mortality associated with diabetes. The Diabetes Control and Complications Trial (DCCT 1983-1993) demonstrated that lowering HgA1C led to significant decrease in rate of micro- and macrovascular complications. As a result of DCCT findings, standards of diabetes care have been developed and adopted by the ADA leading to an approximate 1% reduction in HgA1C levels in both adults and children since results of the study.[4] However, the intensification of insulin regimens and reduction in HgA1C came with increased recognition of low blood glucose levels and subsequent fear of hypoglycemia, especially in pediatric patients. Fear of hypoglycemia has been the major barrier in further reducing HgA1C levels and achieving

euglycemic control. Because of these factors it became obvious that furthering diabetes management technology through improving insulin delivery and glucose monitoring was needed to improve A1C further and decrease rates of hypoglycemia.

advances in diabetes care

We now will examine specific advances in insulin delivery systems, types of insulins, and glucose monitoring devices that are available on the market today that could positively impact glycemic control.

Most patients with new onset type 1 diabetes are still taught how to use traditional insulin syringes and insulin vials, and sent home on multiple dose injection therapy using basal insulin (long-acting insulin) administered once daily with additional analog injections (fast-acting insulin preparations) given before or shortly after meals. Multiple daily injections (MDI) have demonstrated vast improvement of HgA1C levels and in glycemic control in type 1 patients compared to twice daily injections (e.g., NPH and regular insulin in traditional therapy).[4] Most patients on MDI therapy convert to use of insulin pens as they offer portable, faster and precise solutions to delivering insulin. Insulin pen therapy is advancing, now offering devices such as the InPen smart pen. The pen connects via Bluetooth to a smart phone, records insulin usage and makes insulin dose calculations much easier, thereby permitting parents to monitor their child more closely through an app. (Figure 2)

Soon we will see other methods to deliver insulin. An inhaled insulin, Afrezza, is FDA-approved for use in adult patients with type 1 and 2 diabetes. Oral insulin, patch insulin and weekly insulin therapy are currently in development.

Continuous subcutaneous insulin infusion (CSII) therapy via an external pump for the treatment of insulin dependent diabetes has steadily become popular since its invention in the 1970s and with the initial release to the consumer market in the 1990s (figure 3). CSII delivers one type of fast-acting analog insulin via an insulin pump device to a patient through a subcutaneous catheter (plastic or metal). CSII therapy replaces basal insulin (long-acting insulin) with basal rates. CSII therapy also includes meal insulin delivery

figure 2. InPen connects to a smart phone for insulin records and dose calculations

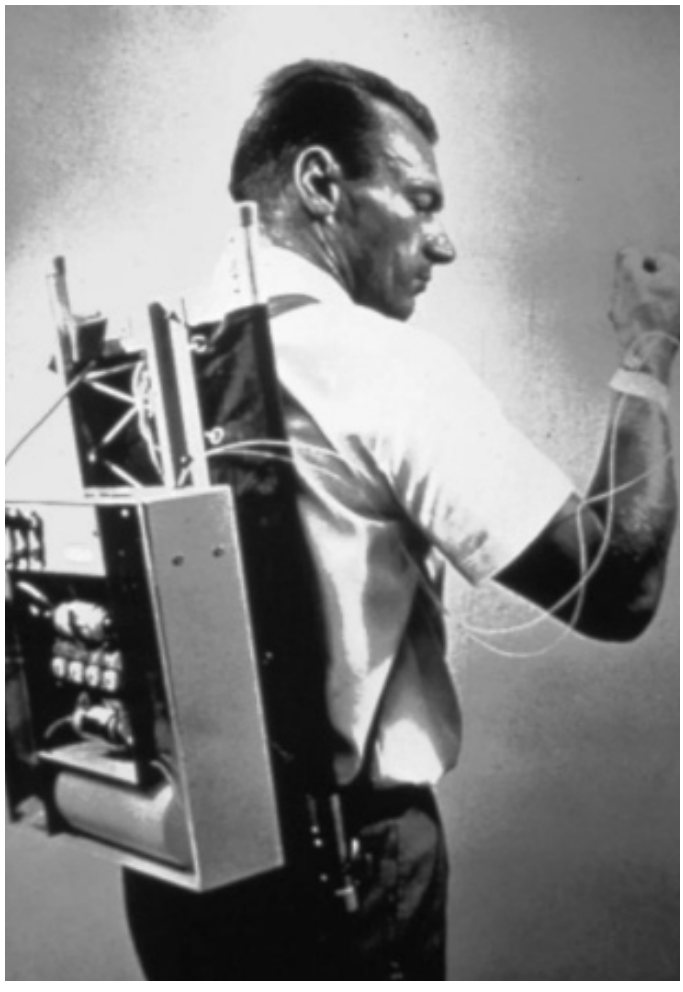

figure 3. Kadish artificial pancreas from the 1960s.

figure 4. External insulin pumps, available on the U.S. market today. From left to right, Omnipod, Tandem t:slim, Medtronic MiniMed.

with analog insulin based on entered glucose level and amount of carbohydrate consumed. CSII therapy is approved in children and adults and especially popular among youngest patients. Since its widespread use in U.S. and European markets, many research studies have demonstrated both decreases in HgA1C levels as well as reductions in hypoglycemia frequency among pump users.[5]

Theoretically CSII therapy could result in an increased frequency of diabetic ketoacidosis (DKA) due to absence of long-acting insulin. If there is interruption in insulin delivery, glucose levels will rise quickly. However, recent data show no higher frequency in DKA among pump users versus MDI users.[6] Infusion site problems such as infections or decreased absorption or tissue hypertrophy are more common among CSII users and rare in injection sites of MDI users. Site rotation, frequent set changes and parental supervision decrease these issues.

Still there is no doubt that CSII pump therapy can be beneficial to type 1 diabetes patients, especially children. Although there is no official recommendation for preferential use of CSII therapy in type 1 diabetes, ADA Standards of Medical Care in Diabetes—2020 state that CSII therapy appears to improve glycemic control and reduce hypoglycemia and should be considered for use in children with type 1 diabetes.[7]

Available insulin pumps vary among consumer markets among European countries and the U.S. Currently in the United States, three CSII delivery systems are approved for use in children, some to be used in children as young as 2 years old (however, even some younger patients could benefit from CSII therapy in some cases). CSII pump devices come in two types. The traditional pump involves plastic tubing that is

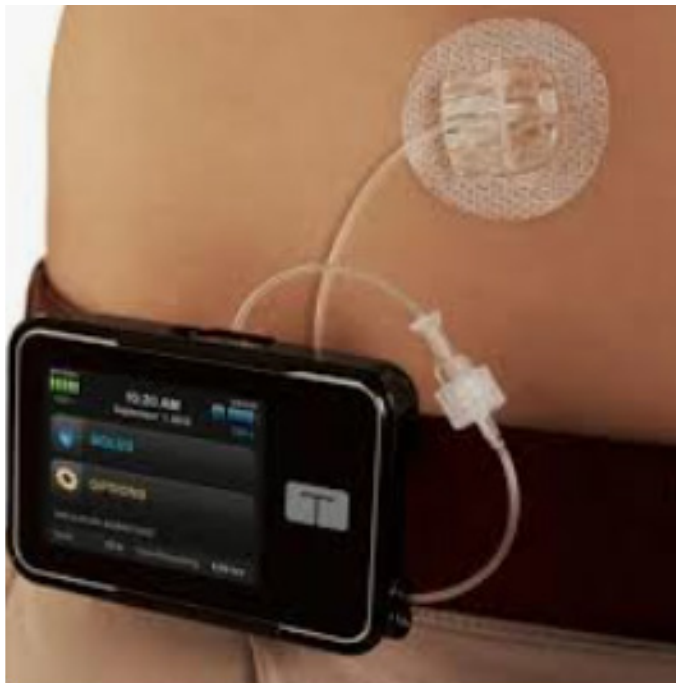

figure 5. Insulin infusion sets attach to wearer subcutaneously

attached to a small storage and control device placed off the body and attached to a patient subcutaneously via an infusion site. Currently two insulin pumps in the U.S. fall into that category: Medtronic MiniMedTM pump and Tandem® insulin pumps (figures 4 and 5). In 2003 an alternative to traditional tube-attached CSII therapy became available to U.S. consumers (manufactured by Insulet). The Omnipod® CSII system is unique and is the first patch pump insulin delivery system. The pod, currently holding up to 200 units of insulin, is filled with analog insulin, placed on the skin and subcutaneously injected into the patient. Infusion sites or pods should be changed every 2-3 days. Separate remote control devices (called PDMs, Omnipod Personal Diabetes Manager) communicate with the pod system

figure 6. Omnipod insulin pump by Insulet. Omnipod is the only tubeless patch insulin pump currently approved by the FDA in the U.S.

via Bluetooth. PDM must be fairly near a wearer and communicates with solely one pod making it impossible to accidently administer insulin to another pod wearer nearby. However, PDM must always be carried in order to deliver bolus insulin for meals and blood sugar correction. The pod itself is bulkier than traditional infusion sites on tubed pumps. But it enables the wearer to not be attached to the pump by catheter. Many parents choose Omnipods for active children who participate in sports or for those who cannot tolerate wired set-ups (figure 6).

Until recently there has been no substantial difference in degree of glycemic control and HgA1C levels among any model or brand of insulin pump. This presently is no longer true. Wired pump devices (t:slim and Medtronic MiniMed) now offer combined systems where insulin delivery is automated at least partially based on information from a continuous glucose monitoring (CGM) device connected to a pump via a Bluetooth transmitter and sensor device. These automated delivery systems adjust preprogramed insulin doses based on blood sugar levels measured and communicated by the CGM system with the goal to increase patient time within a euglycemic range. Older Medtronic systems (670G) use a proprietary sensor called a Guardian 3 sensor. The 670G system, the first partially closed loop or automated insulin delivery system, became available in the U.S. market about four years ago. Studies showed achievement of time spent in range up to 70% of the time resulting potentially in improved glycemic control and decrease in frequency of hypoglycemic episodes (device targets glucose levels at all times to be 70-180mg/dL).[8] Although the pump is approved for use in patients as young as age 7, some of its features make it difficult for use in children. For example, the glucose sensor is not visible to a parent via smart phone making parental supervision of children difficult with distance. The CGM sensor on the Medtronic 670G pump is also not easy to use and still requires periodic (at least twice a day) glucose meter reading called calibrations. This may not be user-friendly for a child or adolescent who does not like to do finger pokes or forgets to do so. The pump automatically can switch from automated insulin delivery mode (automode) to manual mode using the patient's entered insulin dose settings if blood sugar is too low, too high, or if calibration glucose readings are not entered for some time.

Because of these limitations, another model of a Tandem pump (Control IQ) was released on the market in late 2019. It is a CGM integrated with a pump. It is approved for adults and children as young as 6 years. The system requires no glucose calibrations, targets blood glucose levels to 110mg/dl and allows a wearer to increase time spent in range to 80%. The Control IQ offers users insulin boluses administered by the pump automatically if blood sugar is elevated and not corrected by the wearer. This could prove very useful in improving glycemic control among some teenagers and children. The device can provide glucose level information on mobile phone devices or on a receiver display. One can follow blood sugar trends remotely and intervene if blood sugar becomes too low or too high. This feature makes it especially useful in children and increases independence as a

figure 7. Dexcom G6 system makes it easy to monitor blood glucose

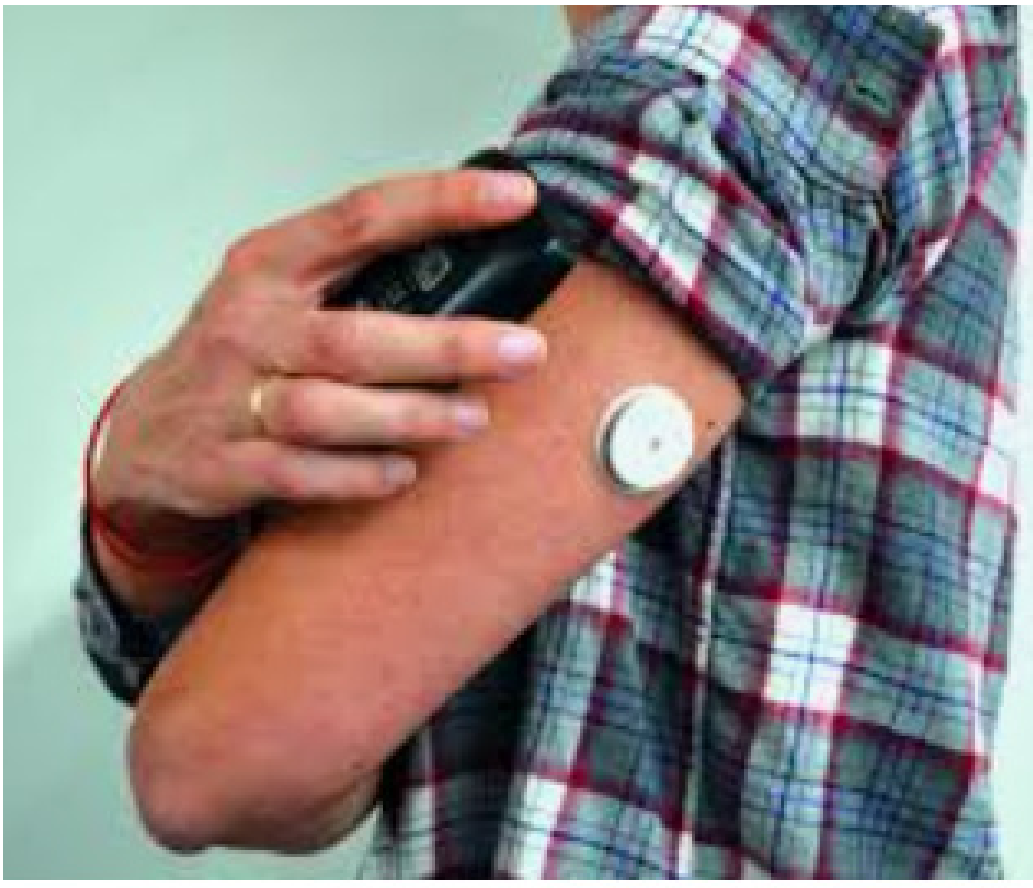

figure 8. FreeStyle Libre 2 system is an easy-to-use 14-day sensor system that allows the wearer to scan a sensor frequently

parent can monitor BG remotely via cell phone data or Wi-Fi (figure 7).

We are far from being done at optimizing glycemic control in diabetic patients. The near future will incorporate even better technologies in daily care of insulin dependent diabetes patients. Automated insulin delivery CGM assisted pump therapy will be standard on every insulin pump soon. As such, the time maintained in glycemic range will increase further and a wearer will soon not need to check blood sugar at all. Eventually one will not need to bolus for food or count carbohydrates consumed improving further both A1C levels and the diabetes patient's quality of life. Nevertheless, it is imperative to note the substantial limitations in the use of pump therapy. Pump therapy can be costly, inclusive of the initial cost of pump hardware and monthly cost of pump supplies. While most commercial insurance plans do cover insulin pump therapy at least partially, these costs make it not very affordable in patients without medical insurance.

Nevertheless, CGM use will continue to improve and expand. DCCT demonstrated that improvement of HgA1C directly depends on how many times glucose level is checked daily (current recommendation 3-6 times). However, that is not a very realistic expectation for many busy patients and parents as it requires time, blood and involves some pain. Continuous glucose monitoring quickly became the standard of care in management of type 1 diabetes. Current ADA pediatric diabetes standards state that CGM should be considered as the form of glucose monitoring for all children with type 1 diabetes.[7] CGM systems on the market can be used without insulin pumps just for monitoring glucose without finger poking. These devices differ a bit in price and features. The least costly and easiest to use CGM monitor is the FreeStyle Libre 2 system that allows the wearer to scan a sensor with a monitor or smart phone (figure 8). Monthly supplies for this system are relatively affordable even for cash paying patients. FreeStyle does not communicate with any insulin pump models as of now. However, most developing insulin pumps are working on incorporating the Libre sensor into pumps. The future will see more CGM devices that are thin, smaller, cheaper, completely disposable and some noninvasive.

conclusion

For a disease that has been treated with insulin for just 100 years, ongoing technological developments have improved glycemic control, decreased complications associated with diabetes, and prolonged life. One can only hope that advances in the future such as islet cell encapsulation and implanting will lead to complete insulin-free life for type 1 diabetes patients.

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Yelena Nicholson, DO, program director

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CME questions

6. When was first patient treated with insulin for type 1 diabetes
   a. 1922
   b. 1945
   c. 1876
   d. 1971
7. Why there is push to intensify control in patients with diabetes
   a. To improve patient quality of life
   b. To decrease complications associated with elevated A1C and poor control
   c. To decrease cost of diabetes care, taxpayer dollars spend and burden on society
   d. All of the above
8. What does auto-maited insulin delivery system involve
   a. Pump that does not require any imput or action from the patient including no carb counting
   b. Pump that improves A1C always by 2%
   c. Insulin pump and glucose sensor that work together to adjust insulin delivery doses based on patients blood sugar to improve A1C and time spend in range
   d. Insulin pen called inpen

navigating the chronic pain journey with children, adolescents and their families

by Kristen Spisak, MD, and Lucinda Brown, DNP, CNS

learning objectives

Following the completion of this article, the reader should be able to:

1. Review the current state of the literature regarding chronic pain including introduction to prevalence, physiology, psychology and family variables that underlie chronic pain and the importance of chronic pain specialists and clinics.
2. Identify resources at Dayton Children's for children and adolescents with chronic pain.

Many health care providers may be surprised to learn that chronic pain in children and adolescents is fairly common and not an unusual diagnosis. An estimated 20-46% of children and adolescents worldwide are affected by various chronic pain disorders. One-third of children and adolescents have some manner of weekly musculoskeletal pain. In comparison, it is estimated that approximately 20% of American adults suffer from chronic pain with two-thirds of those reporting their pain as constantly present and never going away. Fifty percent of adults with chronic pain find it unbearable and excruciating.[1]

Why do children appear to have more chronic pain? The reasons for any perceived or actual increase in the rate of pediatric chronic pain are unknown, though most likely the reasons are multifactorial. Significant reasons may include increased pain identification, stress, anxiety, poor role-modeling and maladaptive pain behaviors and attitudes. Many children with chronic pain also have family members with chronic pain. Perhaps both genetics and the environment play a significant part in children and adolescents developing chronic pain. The Institute of Medicine's report in 2011 on chronic pain proposed that, in many cases, chronic pain is a disease in its own right and therefore demands direct, appropriate treatment.[2] Due to an increased recognition of chronic pain syndromes by both health care providers and the public along with the availability of new treatments, families are more likely to seek potential therapies for conditions that were previously considered untreatable.

The impact of chronic pain on children/adolescents and their families is significant. Many of these patients experience physical, psychological and social sequelae. Chronic pain affects not only the patients but their family and friends, and can significantly alter the family dynamic. Many of these children stop going to school, participating in activities and no longer have friends.

There is also a substantial financial burden on the patient and the family with direct and indirect costs of health care use and lost wages. When considering health care appointments, labs, diagnostics and imaging studies, the costs to the family really start to increase. A 2014 report estimates total health care costs for adolescents with moderate-to-severe chronic pain to be around $19.5 billion annually in the United States alone.[3] In addition, childhood pain is not always an isolated event of growth and development that improves with age. There is evidence that childhood chronic pain predisposes an individual to development of new and different types of pain into adulthood. This is another compelling argument for early and comprehensive treatment for children and adolescents with chronic pain.[4]

physiology, psychology and family variables of chronic pain

Researchers continue to identify information about the pathway of chronic pain. Complex interactions exist between primary afferent nerves, dorsal horn neurons, spinal glia, neurotransmitters and other factors that propagate and perpetuate the symptoms. Most patients present with chronic pain well after the damage from an acute injury has resolved. During an injury, damaged and/or inflamed tissues release growth factors and procytokines, among other neuromediators. The release of neuromediators in the spinal cord activates spinal glia, altering their activity and leading to an increased excitability. Central sensitization with wind-up phenomenon describes this state of dysregulated nociception with increased dorsal horn activity. This activity then triggers an exaggerated response to both painful and non-painful stimuli over a larger anatomic area. Sometimes this process occurs after direct physical injury as mentioned above but also after illness, traumatic psychological events, unrelenting stress and even physical inactivity.[5] The fact that the pain occurs either long after injury or occurs without any injury at all, can be puzzling for both patients and families alike. This entire process is affected by stress, physical activity level, illness and disrupted sleep.[6]

In addition to the physiology of pain, there are numerous psychological characteristics that affect pain. Emotional, cognitive and behavioral factors also significantly influence pain. Emotional and cognitive factors include fear, avoidance of pain, maladaptive strategies for coping with pain, and the influences of anxiousness/depressive symptoms. In addition, parental behaviors regarding pain and cultural expectations are also confounders (figure 1).

It is well known that some youth with chronic pain have premorbid anxiety and depression. Others develop anxiety and depression as a result of their pain. As mentioned earlier, children with this type of pain stop participating in school, sports and extracurricular activities. Discontinuation of these activities leads to loss of positive reinforcement, friendships, lower self-esteem and depression. Anxiety begins to develop due to the missed school and difficulty in keeping up with assignments.

Many children/adolescents also have family with chronic pain. Learned behaviors from these family members significantly impact the meaning of pain and also acceptable coping behaviors when managing pain. Modeling of proper pain coping strategies and minimizing pain distress by the family member with pain helps

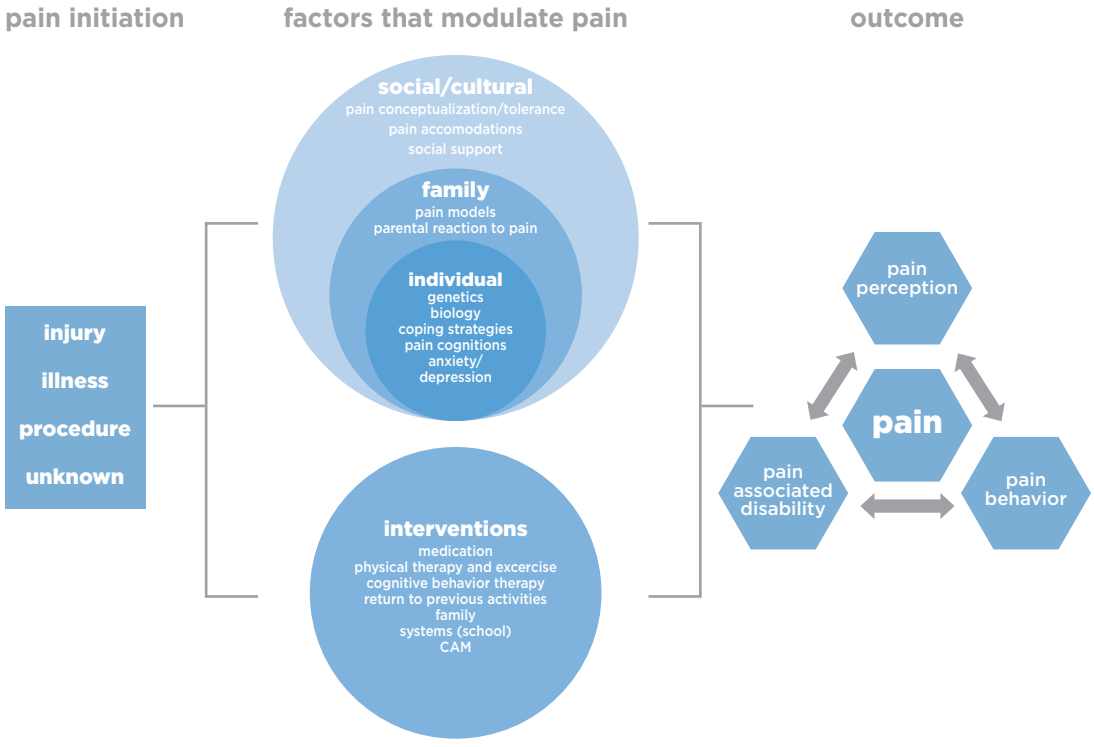

figure 1. Variables that modulate pain

the child/adolescent with their pain management strategies. Conversely, family members who express solicitous responses along with protective behaviors likely increase both the sick role and functional disability.[7]

Chronic pain in children and adolescents is multifactorial and multidimensional. As a result, a multidisciplinary team approach is essential when treating these pain conditions and the treatment plans will vary depending on the diagnosis.

clinical presentations of specific chronic pain conditions

Four common, chronic pain disorders will be briefly reviewed below.

1. Abdominal pain-related functional disorders are among the most common conditions and are estimated to affect 20% of children sometime during their childhood. Most of these diagnoses include irritable bowel syndrome, functional dyspepsia and abdominal migraines. Diagnostic evaluation costs average $6,000 per child. Chronic idiopathic nausea may also be a significant issue with or without abdominal pain. The abdominal pain may also have underlying organ-specific causes such as acid-related disorders, dysmotility, food intolerances and bacterial overgrowth.[1]
2. The prevalence of low back pain may be difficult to ascertain due to the variance in diagnostic criteria. A few studies have identified the prevalence of low back pain to be as high as 40% in adolescents.[1] Girls were more likely to experience low back pain along with whole body pain than boys. Low back pain increases during the adolescent period and reaches adult prevalence around the age of 18. Evaluation of back pain should always include questions about inciting event, quality, duration and location of pain. Red flag symptoms such as constant nighttime or severe pain, abnormal neurological examination, fever, weight loss and trauma must prompt further examination.[1]
3. The identification of juvenile-onset fibromyalgia (JFM) is somewhat challenging, controversial and remains a clinical diagnosis. The American College of Rheumatology guidelines for diagnosis of JFM

focuses on the presence of a variety of symptoms. These symptoms include widespread pain, fatigue and sleep disturbances. Similar to adult fibromyalgia, the etiology of JFM is unknown but is thought to be related to central sensitization in addition to increased sensitivity of the peripheral nervous system. The complexity of the disorder includes other associated symptoms including cognitive fogginess, mood disturbances, migraines, irritable bowel syndrome and dysautonomias. Many JFM patients have difficulties with physical function, decreased quality of life, and greater time spent at home without functioning as a part of society.[1]

4. Joint hypermobility with pain is an increasing cause of overall chronic pain. Hypermobility may be related to various connective tissue disorders but the most common is Ehler-Danlos syndrome (EDS). It is still not known why there is a relationship between hypermobility and pain as some patients with connective tissue disorders have significant pain and some have very little to no pain. The clinical presentations of these patients vary but most exhibit some degree of decreased muscle strength, reduced endurance, impaired function, increased fatigue and impaired quality of life. As with JFM, joint hypermobility is a clinical diagnosis. Some patients may elect to undergo genetic testing, which can be expensive and rarely covered by insurance providers.[1]

treatment options for children/adolescents with chronic pain

A multidisciplinary treatment plan is essential for these pediatric chronic pain patients. Treatment plans vary according to diagnosis, level of functioning, psychological co-morbidities, family involvement and environmental influences.

Pediatric chronic pain clinics are becoming more prevalent and are thought to be the most efficacious way to treat this subset of patients. Pain clinic specialists provide a comprehensive treatment plan that includes medications, physical therapy, psychology and complimentary interventions. A recent study highlights the importance of the pain specialist and clinic in helping children and adolescents manage their pain. The use of the emergency department (ED) as a chronic pain manager is not efficacious and increases the cost of chronic pain to both the family and health care in general. This study examined data for all pediatric patients with an initial visit at an outpatient pediatric pain clinic between 2005 and 2009. Data included patient demographics, insurance type and diagnosis at first pain clinic visit. Rate of health care system utilization three months before and after the initial pain visit was quantified. Approximately 900 patients were included in this study. Overall there were significant decreases in ED utilization and increases in outpatient service utilization after the initial pain clinic visit.[8]

The journey for some children with chronic pain leads to significant disability, and pain associated disability syndrome (PADS) has been well studied. Children and adolescents who don't respond to the treatment plans listed above require a more intensive and coordinated interdisciplinary program. These programs typically include patients as well as family members. The focus of all of these programs is to help the patient return to age appropriate functioning, not reducing pain. Patients are taught strategies that include relaxation, positive thinking, sleep hygiene and stress management. Physical and occupational therapy aim to help patients become more physically active so that the patients return to homework, chores, and other age-appropriate activities like playing sports and participating in other extracurricular activities. Medical management providers evaluate patients for medications that may help; however, patients are informed that medications may only help with 30-40% of the pain. Topical creams/solutions, anticonvulsants, antidepressants and muscle relaxers are commonly used as part of a multimodal treatment plan. Opioids are not indicated for the management of chronic pain.[1]

Pediatric chronic pain treatment programs occur in outpatient and inpatient settings. Outpatient treatment settings typically include parental participation. Inpatient settings often separate the family and child for periods of time during the rehab process. This separation reduces secondary gain and allows the patient to learn new pain management strategies without family influence. These programs have been available in the adult population for some time but limited data is available in the pediatric population. However, this data suggests that the patients attending these programs report significantly improved function, decreased depression and healthier thoughts about their pain.[1]

Dayton Children's chronic pain clinic and chronic pain program

After 12 months of planning, the chronic pain clinic at Dayton Children's opened at the south campus in April 2019. The chronic pain clinic falls under the division of anesthesia and the program director is Kristen Spisak, MD.

philosophy of the chronic pain clinic

Chronic pain is defined as pain that has lasted for at least three months and/or is out of proportion to the event causing the pain. Chronic pain is best managed by a comprehensive team approach that includes medications, physical therapy, psychology, interventional procedures and complementary therapies. Medication management may include oral or topical formulations.

The following team members are involved:

Providers
Kristen Spisak, MD;
Cindy Brown, DNP;
Brianne Fitzgerald, FNP

Psychology
Jackie Warner, PhD;
Erin Webster, PhD;
Latisha Gathers, PsyD

Physical therapy:
Sam Schwendeman, DPT;
John Steiner, DPT

Scheduler:
Dana Kenyon

Pharmacy:
Ashley Clark, PharmD

Child life, social work and nutrition:
by request of pain team staff

The chronic pain clinic sees children and adolescents until the age of 22 years (patients then transition to an adult pain provider as appropriate) who experience all types of chronic pain including but not limited to fibromyalgia, juvenile rheumatoid arthritis, Ehler-Danlos syndrome, musculoskeletal, abdominal, post-traumatic, post-orthopedic procedure, post-surgical procedure, oncology-based and sickle cell disease. Patients with migraines are cared for by neurology.

Recent data indicates that 167 patients are being evaluated at the chronic pain clinic. Ages range from 5-22 years of age and most common diagnoses include chronic pain syndrome, low back pain, fibromyalgia and general myalgias (tables 1 and 2, figure 2).

In addition, the pain clinic offers a comprehensive rehab program that spans weekly visits over eight weeks. The program focuses on providing multidisciplinary therapy to patients with chronic pain with the goal of improving quality of life and facilitating a return to regular daily activities. The focus of this therapy does not include the "why" of pain but instead focuses on the "how" to get back to a normal life. Our program focuses on helping patients learn about aspects of their pain and life that they can control when a cure is not possible. Various types of treatment and therapies are presented to help each patient in returning to an active and fulfilling life. Our program is unique in that separate group sessions are required for family members so that they also learn how to work with their child during their pain journey. Since inception, our clinic has offered approximately nine 8-week cohort sessions with an average of four to eight patients in each cohort. The evaluations from patients and family have been very positive. We continue to see many patients at three-to-six-month follow-up intervals and overall function has increased for most patients. Ongoing data collection is still in process and more detailed information about the success of this program will be available in the future.

general statistics			
	unique patients	average # of visits/patient	range of visits/ patient (min-max)
FY20	106	3	1-14
FY21	61	2	1-8

table 1. Patient data regarding visits

age range of patients	unique patient count
5-10	4
11-15	35
16-10	63
21+	15

table 2. Age ranges of patients

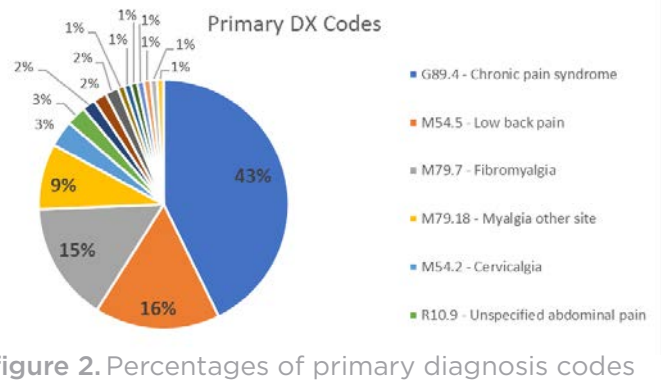

figure 2. Percentages of primary diagnosis codes

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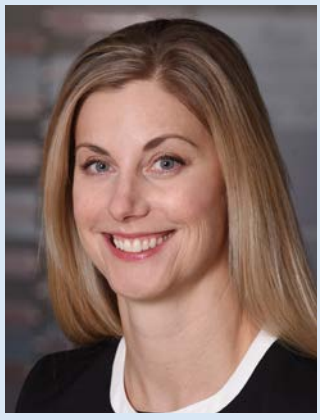

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CME questions

9. **Chronic pain is a common occurrence in children and adolescents and actually found more frequently than in the adult population.**
   a. **True**
   b. **False**
10. **The impact of chronic pain is significant for children and adolescents as it:**
   a. **Causes physical and psychological sequelae but doesn't affect the social environment of the patient**
   b. **Often creates a significant financial burden for the family**
   c. **Is challenging during the patient's younger years but typically resolves by adulthood**
11. **One of the benefits of using a pain specialist in a clinic includes:**
   a. **Decreasing the amount of emergency department visits for chronic pain**
   b. **Establishing a multidisciplinary treatment plan**
   c. **Decreasing the amount of opioid medications that are used**
   d. **All of the above**

COVID-19 update

by Sherman J. Alter, MD

This article will briefly examine both some recent COVID-19 literature and recommendations of importance to the pediatric health care provider.

learning objectives

Following the completion of this article, the reader should be able to:

1. Review risk factors for severe disease and rates of hospitalization in children and adolescents with COVID-19.
2. Discuss the infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children.
3. List recommendations for travel in individuals fully vaccinated with COVID-19 vaccines.

The American Academy of Pediatrics and the Children's Hospital Association continue to summarize publicly reported child and adolescent COVID-19 data (49 states, New York City, District of Columbia, Puerto Rico, and Guam). As of April 15, 2021, there have been 3,631,189 total child COVID-19 cases reported. Children represented 13.6% of all cases. The overall rate in these areas was 4,824 cases per 100,000 children in the population. Children were 1.3%-3.0% of total reported hospitalizations, resulting in 0.1%-1.9% of all child COVID-19 cases being hospitalized. Children were 0.00%-0.21% of all COVID-19 deaths, and 10 states reported zero child deaths.[1] As reflected in the data, infection in the pediatric population is comparatively much less than the infection rates noted among older groups. Nonetheless, serious illness can arise in these younger age groups.

COVID-19 in the pediatric population

The CDC recently reviewed COVID-19 among children.[2] The study collected discharge information from 869 medical facilities from March 1 to October 31, 2020. Of 20,714 US children with COVID-19, more than 1 in 10 were hospitalized, of whom 31.1% (756) had severe COVID-19 (requiring admission to the intensive care unit, mechanical ventilation, or comparable treatment). Seven percent required mechanical ventilation. The study found that 2,430 (11.7%) of the 20,714 children who had an emergency department or inpatient encounter were hospitalized with COVID-19.

Girls were more likely to be hospitalized (52.8%) as were those aged 12 to 18 years. Over half (53.8%) of hospitalized children had at least one chronic condition. Similar to COVID studies in adult populations, Hispanic and Black populations were overrepresented at 39.3% and 24.4%, respectively. However, when looking at factors for severe COVID-19, neither race nor insurance type had any significant associations.

Children and adolescents who had a pre-existing chronic health condition were three times more likely to develop severe disease when compared to youths who were healthy (adjusted odds ratio [aOR], 3.27; 95% confidence interval [CI], 2.44 to 4.37). Male patients had higher occurrence of severe disease (aOR, 1.52; 95% CI, 1.26 to 1.83). The likelihood of severe illness also increased if the child was 2 to 5 or 6 to 11 years of age versus a teenager (aORs, 1.53 for both; 95% CIs, 1.11 to 2.13 and 1.04 to 2.23, respectively).

Severe illness due to COVID-19 remains infrequent among children. As remarked by the investigators, "Although admission to an intensive care unit for younger children may indicate an abundance of caution by clinicians or facility and administrative requirements rather than disease severity, this finding has important clinical and resource planning implications for facilities and clinicians. Understanding factors associated with severe COVID-19 disease among children could help inform prevention and control strategies."

infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children

Nasopharyngeal swabs were collected from adult and pediatric cases of COVID-19 and from their contacts who tested positive for SARS-CoV-2 in Manitoba, Canada, between March and December 2020. Viral growth in cell culture, cycle threshold values (CT-an indirect measure of viral concentration) from reverse transcription polymerase chain reaction (RT-PCR), and quantitation of virus in tissue culture were compared in adults and children.[3]

Among 305 samples positive for SARS-CoV-2 by RT-PCR, 97 samples were from children < 10 years of age, 78 were from children aged 11–17 years and 130 were from adults (≥ 18 years). Viral growth in culture was present in 31% of samples, including 18 (19%) samples from children 10 years or younger, 18 (23%) from children aged 11–17 years and 57 (44%) from adults (children v. adults, aOR 0.45, 95% CI 0.28–0.72). Children with NP swabs that tested positive for SARS-CoV-2 had higher PCR cycle thresholds (suggestive of less virus) and lower viral concentrations in tissue culture. Because children were less likely to grow virus in culture, had higher PCR cycle thresholds and lower viral concentrations, these findings along with other epidemiologic features noted during the pandemic suggest that children are less capable of transmitting infectious virus and likely are not the main drivers of SARS-CoV-2 transmission. Daycare, in-person school and cautious extracurricular activities might be safe to continue with appropriate precautions in place, and with lower risk to child care staff, educators and support staff than initially envisaged.

travel

As more individuals are vaccinated with COVID-19 vaccines, more persons are protected from acquiring infection with the SARS-CoV-2 virus. Based on what we know about COVID-19 vaccines, those who have been fully vaccinated can start to do some things that they had ceased doing because of the pandemic. Remember that an individual is considered fully vaccinated two weeks after the second dose of mRNA vaccines (Pfizer or Moderna) or two weeks following a single-dose vaccine (Johnson & Johnson). Until we know more, one should continue

precautions in public places to minimize transmission of the virus – wear a mask, stay 6 feet apart from others, wear masks, maintain physical distancing, and practice other prevention measures when visiting unvaccinated persons, and avoid medium- and large-sized crowds or poorly ventilated spaces. Moreover, one should get tested if experiencing COVID-19 symptoms even if fully vaccinated.

The following interim recommendations from the CDC, however, can guide decisions about daily activities and travel after one is fully vaccinated.[4] These recommendations apply to non-health care settings.

If fully vaccinated, one may:

- Visit inside a home or private setting without a mask with other fully vaccinated people of any age
- Visit inside a home or private setting without a mask with one household of unvaccinated people who **are not at risk for severe illness**
- Travel domestically without a pre- or post-travel test
- Travel domestically without quarantining after travel
- Travel internationally without a pre-travel test depending on destination
- Travel internationally without quarantining after travel

If fully vaccinated, one may not:

- Visit indoors, without a mask, with people who **are at increased risk for severe illness** from COVID-19
- Attend medium or large gatherings

If a person has been around someone who has COVID-19, he does not need to stay away from others or get tested unless symptoms of COVID-19 develop.

The pandemic is just over one year old. We will continue to learn more about immune protection with increasing vaccination rates and with the emergence of SARS-CoV-2 viral variants. We can look forward to expansion of COVID-19 vaccines in the pediatric population (and we must maintain efforts to immunize children with all recommended vaccines). There will be further advances in the prevention and management of COVID-19 infections. All will be eagerly following these developments as the months roll on.

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Dayton Children's updates

Dayton Children's Hospital announces construction of five-story, specialty care outpatient center

Dayton Children's Hospital announced the construction of a new, five-story specialty care outpatient center projected to open in 2023 at the hospital's main campus. The $78 million construction project includes four floors for outpatient clinic space and fifth floor shell space for a total of 152,000-square feet. The building will be where the Cox building was previously located.

"Our vision to reinvent the path to children's health starts within our own walls. We must have facilities that reflect our vision and support our hospital's mission to provide optimal care for every child within our reach," said Deborah Feldman, president and CEO of Dayton Children's. "Critical to our reinvention is superior consumer access, an exceptional total experience and innovative, collaborative care models. This new center will allow us to continue to deliver the world-class care that our patients and families have come to expect from Dayton Children's."

The goal of the new center is to match Dayton Children's inpatient experience, which was transformed by the 2017 opening of the patient tower, in the outpatient care setting at the hospital's main campus.

The new space will provide the conveniences families are seeking in an outpatient setting—close-by surface parking, imaging and pharmacy services just steps away from clinics, and fully integrated orthopedic and sports medicine services with rehabilitation. Moreover, the design of this new facility will enable the holistic, multidisciplinary care required to improve health outcomes and enable the flexibility and efficiencies needed to reduce appointment wait times and improve access to specialty care, whether in person or virtual.

"This is a huge milestone in the history of the hospital. It's also a huge milestone for the Dayton community," said Feldman. "When we formulated our campus renewal plan, we made a commitment to the region to continue to renew our facilities on Valley Street for future generations of children needing our care. We are fulfilling that promise."

To take on this important project, the hospital re-enlisted Cannon Design/FKP and Champlin Architecture and Danis Construction, the firms responsible for architectural design and construction management of the hospital's patient tower in June 2017. Construction of the new facility has already begun.

Dayton Children's Hospital receives the 2021 Women's Choice Award® as a Best Children's Hospital

Dayton Children's Hospital has been named as a Best Children's Hospital by the Women's Choice Award®, America's trusted referral source for the best in health care.

"Our Best Children's Hospitals award raises awareness of the top quality care offered for children. The best hospitals embrace families as an integral part of healthcare and improving children's outcomes." said Delia Passi, CEO and founder of the Women's Choice Award.

The list of 38 award winners, including Dayton Children's Hospital, represents hospitals that have met the highest standards for childcare.

"At Dayton Children's, families know we treat their children as if they are our own," says Deborah A. Feldman, president and CEO of Dayton Children's Hospital. "We are honored that the Women's Choice Award proves that trust."

get to know the center for the female athlete

The center for the female athlete will empower young female athletes to nurture the best version of themselves. We will focus on delivering a comprehensive program that is unique to the female athlete and the changes she faces in her athletic and personal life. Her experience is individual to her and will be shaped by interactions with us, both digitally and in person. We will create a holistic approach to her care while focusing on exercise habits, hormonal balance, nutrition and counseling support to enable optimal health and teach her healthy habits. We will equip her with the tools she needs to be her unique self. This program will be focused on the female athlete as a whole person. ***Her takeaway: I have the power.***

what is the center for the female athlete?

The center for the female athlete is led by a group of physicians, specialists, dietitians, and athletic trainers dedicated to the current and future health and wellness of the female athlete.

Caring for young female athletes provides an underrepresented opportunity to focus on total wellness and provided access to many clinical tools for helping young, active, teen girls develop a foundation for health and wellness now and for many years to come.

Girls who enter the center for the female athlete will participate in an integrated care model that assesses them holistically.

This program is not focused solely on performance or injury recovery and prevention, but rather on the total wellness of the young female athlete and the unique situations that affect the female athlete.

who should be referred to the center for the female athlete?

We see patients ages 13-18 for a variety of conditions such as:

- Nutritional concerns
- Sport specific injury prevention
- Bone health and bone density testing
- Risk assessment for the RED-S female athlete triad
- Mental health screening
- Performance anxiety/body image issues
- Recurrent injuries

how can I learn more about the center for the femaie athlete?
For all the information you need about the center for the female athlete, visit: **childrensdayton.org/centerforthefemaleathlete**

program evaluation

1. The material presented in this publication met the mission to enhance health care delivery in our region through education based on the essentials and policies of the Accreditation Council for Continuing Medical Education.
   ☐ Strongly agree ☐ Agree ☐ Neutral
   ☐ Disagree ☐ Strongly disagree

2. Did the material presented in this publication meet the educational objectives stated?
   ☐ Yes ☐ No

3. Did the material presented in this publication have a commercial bias?
   ☐ Yes ☐ No

4. Please rate the contents of this issue using the following scale:
   1 = Poor, 2 = Fair, 3 = Good, 4 = Very good, 5 = Excellent *(Circle one response for each.)*

	Poor				Excellent
Timely, up-to-date?	1	2	3	4	5
Practical?	1	2	3	4	5
Relevant to your practice?	1	2	3	4	5

5. Please describe any changes you plan to make in your clinical practice based on the information presented in this program.

   _____

6. Are there any other topics you would like to have addressed in this publication or future educational programs for health care providers?
   ☐ Yes ☐ No If yes, please describe:

   _____

7. Please describe how you will incorporate information obtained from this publication into your practice.

   _____

8. Letter to the editor — Letter to the editor may be emailed to alters@childrensdayton.org or attached to this evaluation and may be published in the next issue.

physician accreditation statement and credit designation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Wright State University (WSU) and Dayton Children's Hospital.

WSU designates this Journal-based CME Activity for a maximum of 4 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

program test

to obtain CME credit you must:

Read and reflect on each article.

Answer the questions from each article and complete this test — http://cmequiz.childrensdayton.org/Winter2021PedForum. 70 percent correct answers are needed to obtain the full 4.0 AMA PRA Category 1 Credits™.

Complete the program evaluation.

Return your completed test and program evaluation by email, mail or fax to: Sue Strader, coordinator
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pediatric forum | volume 34, issue 1

your answers to CME questions
(Please circle the BEST answer.)

1.	a	b	c	d
2.	true	false		
3.	true	false		
4.	true	false		
5.	true	false		
6.	a	b	c	d
7.	a	b	c	d
8.	a	b	c	d
9.	true	false		
10.	a	b	c	
11.	a	b	c	d

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pediatric forum

may 2021

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The purpose of Pediatric Forum is to provide information and news about pediatric health care issues and to provide information about clinical services and management issues of Dayton Children's.

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To obtain CME credit, read, reflect on articles, complete the evaluation and answer at least 70 percent of the quiz correctly. Send the answer sheet and program evaluation to:

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target audience

This education activity is designed for pediatricians, family physicians and related child health care providers.

educational objectives

- Identify the four pediatric issues covered in this journal and develop appropriate intervention.
- Appropriately use the resources of Dayton Children's Hospital to improve patient care.

dayton children's

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