Pediatrics in Review®

AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS



APRIL 2025
Vol. 46 No. 4
www.pedsinreview.org

Impact of Natural Disasters on Children: Key Considerations for Pediatricians

Food Introduction in Infancy

A Review of Wilms Tumor

In Brief

Prevention Strategies for RSV Infection in Infants

Inflammatory Markers in Pediatrics

Visual Diagnosis

Multiple Painless Papules in the Oral Cavity of a 4-Year-Old Boy

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

Pediatrics in Review

Editor-in-Chief
Joseph A. Zenel, *Bend, OR*

Deputy Editor
Hugh D. Allen, *Houston, TX*

Associate Editor, Index of Suspicion
Peter F. Belamarich, *New York, NY*

Associate Editor, Visual Diagnosis
Mark F. Weems, *Memphis, TN*

Associate Editor, In Brief
Janet R. Serwint, *Baltimore, MD*

Associate Editor, In Brief
Linda Y. Fu, *Washington, DC*

Associate Editor, CME
Rani Gereige, *Miami, FL*

Corresponding Editor
Kriti Puri, *Houston, TX*

Managing Editor
Heidi Willis

Editorial Associate
Josh Sinason

EDITORIAL BOARD

Eyal Ben-Isaac, *Los Angeles, CA*
Roger L. Berkow, *Atlanta, GA*
Rebecca C. Butterfield, *Albany, NY*
Heather Campbell, *Washington, DC*
Cynthia Christy, *Rochester, NY*
Steven Ciciora, *Columbus, OH*
Walter N. Dehority, *Nashville, TN*
Cleavon Covington, *Galveston, TX*
Daniel M. Fein, *Bronx, NY*
Marc D. Foca, *Bronx, NY*
Naomi Fogel, *Chicago, IL*
John G. Frohna, *Charleston, WV*
Timothy Garrington, *Aurora, CO*
Tamara Gayle, *Washington, D.C.*
Bert Emil Johansson, *El Paso, TX*
Marta King, *Saint Louis, MO*
Stephanie Lauden, *Columbus, OH*
Priya Mahajan, *Mission Viejo, CA*
Katie A. Meier, *Cincinnati, OH*
Elizabeth A. Ng, *Farmington, CT*
Elaine M. Pereira, *New York, NY*
Norman Ramirez-Lluch, *Mayaguez, PR*
Jennifer A. Reed, *Sioux Falls, SD*
Nicholas Stetkevich, *Houston, TX*
Kanani Titchen, *San Diego, CA*
Samantha Vergano, *Norfolk, VA*
Melissa Weddle, *Portland, OR*
Shan Yin, *Cincinnati, OH*
Shabana Yusuf, *Houston, TX*

PUBLISHER American Academy of Pediatrics

Susan J. Kressly, President

Mark Del Monte, Chief Executive Officer/Executive Vice President

Mark Grimes, Vice President, Publishing

Joseph Puskarz, Director, Journal Publishing

The journal wishes to extend special thanks to the following question writers and ancillary reviewers who contributed to this issue:

Theresa Bingemann, MD
Sydney Rice, MD, MS
William Walker, MD

CME/MOC INFORMATION:

The American Academy of Pediatrics (AAP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The AAP designates this journal-based CME activity for a maximum of 36.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

In order to earn CME credits and/or ABP MOC Part 2 points, you must participate in this activity online at www.pedsinreview.org, where you will view additional information, complete your CME quizzes, and claim credit online.

The American Academy of Pediatrics is committed to principles of equity, diversity, and inclusion in its publishing program.

ARTICLES

189 Impact of Natural Disasters on Children: Key Considerations for Pediatricians
Alexis Cordone, Victoria Fairchild, Mark X. Cicero

198 Food Introduction in Infancy
Cleavon Covington, Fiona Adame, Joanne Acevedo, Meredith Suggs

206 A Review of Wilms Tumor
Valeria Smith, Andrew Wahba, Murali Chintagumpala, Priya Mahajan

INDEX OF SUSPICION

213 Torticollis and Hypoxia in a Febrile 3-Year-Old Girl
Roselyn Appenteng, Lauren K. Kahl

216 Jaundice Developing in a 13-Day-Old Baby With Down Syndrome
Shane Clark, Annette Roberts, Paul Suhocki, Samrat Das

219 Chest Pain and Weight Loss in a 10-Year-Old Girl
Helen Zhou, Alvin P. Chan, Alireza Sedarat, Esther Jun-Ihn

224 Purulent Right Ankle Wound in a 3-Year-Old Boy
Jose A. Elizondo-Leal, Brenna Parker, Rebecca C. Brady, Melissa D. Klein

IN BRIEF

228 Prevention Strategies for RSV Infection in Infants
Shannon Glenn-Otto, Adam Dziacky

231 Inflammatory Markers in Pediatrics
Lingxiao Viviano, Margaret Huntwork

VISUAL DIAGNOSIS

e14 Multiple Painless Papules in the Oral Cavity of a 4-Year-Old Boy
Victor N. Oboli, Dyuti Kumar, Blessing Adanda Chuku, Magda Mendez



To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.



CONNECT WITH US ON SOCIAL MEDIA



Answer Key appears on page 230.

Pediatrics in Review® (ISSN 0191-9601) is owned and controlled by the American Academy of Pediatrics. It is published monthly by the American Academy of Pediatrics, 345 Park Blvd., Itasca, IL 60143.

Statements and opinions expressed in *Pediatrics in Review*® are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees. Recommendations included in this publication do not indicate an exclusive course of treatment or serve as a standard of medical care.

Subscription price for 2025 for print and online/online only: AAP/CPS Member $242/$185; AAP National Affiliate Member $190/$139; Nonmember $298/$236; AAP In-training Member $190/$139; Nonmember In-training/Allied Health $216/$159. Institutions call for pricing (866-843-2271). For overseas delivery, add $120. Current single issue price is $22 domestic, $25 international. Replacement issues must be claimed within 6 months from the date of issue and are limited to three per calendar year. Periodicals postage paid at ARLINGTON HEIGHTS, ILLINOIS and at additional mailing offices.

© **AMERICAN ACADEMY OF PEDIATRICS, 2025. All rights reserved.**

Printed in USA. No part may be duplicated or reproduced without permission of the American Academy of Pediatrics.

POSTMASTER: Send address changes to PEDIATRICS IN REVIEW®, American Academy of Pediatrics Customer Service Center, 345 Park Blvd., Itasca, IL 60143.

Impact of Natural Disasters on Children: Key Considerations for Pediatricians

Alexis Cordone, MD, Victoria Fairchild, MD, Mark X. Cicero, MD

Section of Pediatric Emergency Medicine, Departments of Emergency Medicine and Pediatrics, Yale University School of Medicine, New Haven, Connecticut

PRACTICE GAPS

Natural disasters have dramatic negative impacts on children, both physically and psychologically; pediatricians need to be able to appreciate the risks of the specific natural disasters to which the community they serve is vulnerable and to offer mitigation strategies during these times of need.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the negative impacts of natural disasters on children's physical and mental well-being.
2. Identify disaster-related stressors that families may experience and provide resources and needed support.
3. List demographic and socioeconomic factors of children and families associated with vulnerability and resiliency during disasters.

INTRODUCTION

Natural disasters, defined as catastrophic events triggered by the Earth's natural processes, can profoundly disrupt human lives, communities, and ecosystems. These events include hurricanes, floods, earthquakes, tsunamis, wildfires, blizzards, and volcanic eruptions, among others. Accelerated by climate change, the frequency and severity of these disasters are on the rise, posing an increased threat to global health and stability. The impact of natural disasters extends beyond the immediate physical injuries and fatalities, leading to a cascade of secondary health detriments and a host of socioeconomic challenges.[1]

Children, with their unique physiologic, psychologic, and developmental needs, are particularly vulnerable to the consequences of natural disasters. Effective management strategies must extend beyond the acute phase to integrate immediate and sustained medical, psychologic, and social support, mitigation, and preventive and preparation measures. By emphasizing preventive measures, acute care, and comprehensive long-term recovery processes, pediatricians play a pivotal role in ensuring that the needs of children are prioritized amidst the increasing frequency and severity of natural disasters.[1]

AUTHOR DISCLOSURE: Drs Cordone, Fairchild, and Cicero have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ED	emergency department
FEMA	Federal Emergency Management Agency
NIMS	National Incident Management System
SO	Incident Commander and a Safety Officer
START/JumpSTART	Simple Triage and Rapid Treatment
PsySTART	Psychological Simple Triage and Rapid Treatment

COMMONLY ENCOUNTERED DIAGNOSES

In the aftermath of natural disasters, children face a myriad of health and welfare challenges that span physical, psychologic, and social spectrums. This section gives an overview of the consequences children face after natural disasters.

Physical Injuries

Children are particularly susceptible to physical injuries during natural disasters, including fractures, lacerations, contusions, and head injuries due to falling debris or evacuation efforts. Crush injuries and traumatic brain injuries may occur secondary to collapsing structures, particularly in the setting of earthquakes.[2] The risk of drowning incidents escalates significantly in the case of floods and tsunamis, leading to potential hypoxia and long-term neurologic, respiratory, and other end-organ consequences. Burn injuries, eye injuries, and inhalational injuries can be seen, particularly in the context of wildfires. Injuries frequently encountered in specific types of disasters are shown in Table 1.[3–10]

TABLE 1. Commonly Encountered Physical Injuries by Natural Disaster Type

Natural Disaster Type	Injury Type	Examples From Specific Natural Disasters
Earthquake	Crush injuries, fractures, head injuries, and lacerations	2010 Haiti Earthquake: most common injury diagnoses included fractures and dislocations; wound infections; head, face, and brain injuries; burns; and crush injuries[3]
Hurricane	Drowning, hypothermia, carbon monoxide poisoning, and toxic chemical spills	2005 Hurricane Katrina: over one-third of deaths caused by drowning[4]
Tornado	Crush injuries, blunt trauma, fractures, and lacerations	2016 Jiangsu Tornado in China: soft tissue injuries and fractures among the most common injuries[5]
Flood	Drowning, hypothermia, and electrocution	2017 South Asian floods: over 1300 deaths from flood-associated injuries including drowning and electrocution[6]
Wildfire	Burns and smoke inhalation	2023 Canadian wildfires: common injuries included burns, smoke inhalation, and trauma from rapid evacuation processes[7]
Volcano	Burns and ash and/or smoke inhalation	1980 Mount St. Helens eruption: asphyxiation, thermal injuries, and respiratory distress syndrome[8]
Landslide	Crush injuries, blunt trauma, and suffocation	2018 Montecito Debris Flow: among admitted patients, the most common injuries were soft tissue injuries, hypothermia, craniofacial injuries, and orthopedic injuries[9]
Tsunami	Drowning and hypothermia	2011 Japan Tsunami: approximately 20 000 deaths, largely from drowning[10]

Infectious Diseases

The displacement of populations after a natural disaster often results in overcrowded living conditions in shelters, facilitating the spread of respiratory and gastrointestinal tract infections. The spread of viruses such as rotavirus, enterovirus, and norovirus are markedly increased under these conditions.

Rotavirus causes severe diarrhea, particularly dangerous for young children in these stressful environments. Enteroviruses can lead to various symptoms, from mild respiratory issues to severe neurologic conditions, worsened by the close quarters in shelters. Norovirus, highly contagious and known for causing outbreaks of gastroenteritis, can sweep through displaced populations quickly when hygiene and sanitation are compromised.

After hurricanes and floods, surges of waterborne diseases including cholera and leptospirosis may be seen due to contaminated water. For example, the extreme weather conditions caused by Hurricanes Irma and Maria in 2017 disrupted water sanitation practices in the US Virgin Islands, which is believed to have contributed to the first reported cases of human leptospirosis in the region.[11] Standing water can also escalate the incidence of vector-borne diseases, including malaria and dengue fever. Vaccine-preventable diseases may be encountered with increasing frequency due to the breakdown of normal sanitation and health care services in combination with overcrowding.[12]

Nutritional Concerns and Food Insecurity

Natural disasters can cause disruptions at any point in the food supply chain, including production, handling and storage, processing, and distribution. These disruptions can lead to food insecurity, hunger, and malnutrition.[13] Protein-energy malnutrition is an existing problem in many low- and middle-income countries that may be exacerbated by the occurrence of natural disasters, resulting in more severe and widespread cases. Specific phenotypes of protein-energy malnutrition may be encountered, including marasmus (featuring abdominal protuberance) and kwashiorkor (notable for generalized edema). Micronutrient deficiency may become more prevalent in the wake of natural disasters secondary to the lack of diversified food sources and may result in various diseases, including iron-deficiency anemia, zinc deficiency, vitamin A–deficiency blindness,

beriberi, pellagra, edema, and goiters.[14] The long-term impacts of such are significant and can have profound effects on a child's physical health, mental health, and development.

Mental Health Concerns

Natural disasters adversely impact the mental health of children. Posttraumatic stress disorder, anxiety, depression, and other mental health issues are commonly seen in the aftermath of all disaster types. Further, displacement and the loss of caregivers, family, or other loved ones contributes to a sense of instability and insecurity.[15] In the 2023 Maui wildfire's aftermath for instance, many children faced severe anxiety and trauma from the destruction of their homes and communities, coupled with the emotional toll of losing loved ones and the stress of displacement. This and similar events have led to a heightened need for mental health support services to help children cope with the profound impacts of disasters.[16]

One tool used during the Maui wildfires that may be helpful in the wake of other disasters is the Psychological Simple Triage and Rapid Treatment (PsySTART) triage system. This tool, which is a means for performing rapid mental health triage, aims to identify children at risk for traumatic stress and other mental health issues after disasters. By rapidly assessing the psychologic impact on children, PsySTART may help allocate mental health resources effectively, ensuring timely and appropriate support for those affected.[17,18]

Exacerbation of Chronic Conditions

Children with chronic health conditions, such as sickle cell disease, diabetes, or congenital heart disease, may experience exacerbations due to the stress of the disaster itself, interruptions in treatment, or exposure to environmental triggers. Infrastructure breakdown can lead to challenges with accessing medications or medical equipment.[19] Particularly vulnerable children include those reliant on dialysis and infusions for health maintenance. Likewise, children with asthma are at risk of exacerbation if they lack access to controller and rescue medications, especially if other precipitants, such as smoke exposure, are present during the natural disaster. For example, the Canadian wildfires in 2023 led to a significant increase in emergency department (ED) visits for asthma exacerbations. According to a US Centers for Disease Control and Prevention report that analyzed data from the National Syndromic Surveillance Program, ED visits for asthma were 17% higher than expected during 19 days of wildfire smoke from April to August 2023.[20]

Educational Disruption

Natural disasters often result in prolonged school closures, interfering with education and social development. For example, the Huffington Post reported that "In the aftermath of Hurricane Katrina, approximately 118 000 school-aged children in Louisiana and 20 000 school-aged children in Mississippi were displaced."[1] Many children did not attend school for multiple years after displacement.[21,22] The loss of routine, social isolation from peers, and the interruption of learning contribute to emotional distress and can have long-term implications for academic achievement and developmental milestones.

Addressing the multifaceted impact of natural disasters on children requires a focused, multidisciplinary approach that integrates pediatric health care, mental health support, and social support. Effective disaster response must prioritize these elements to ensure equitable recovery and build resilience among the most vulnerable.

MANAGEMENT

The disaster cycle describes the steps taken in preparation, response, recovery, and mitigation for a disaster (Figure 1).

Acute Response

When a pediatrician is part of the initial disaster response team, the immediate priority is to ensure the safety of the responding team. The pediatrician should coordinate with local authorities whenever possible. In areas with robust infrastructure and planning, oftentimes, an Incident Commander and a Safety Officer (SO) will be appointed, and the pediatrician should relay any concerns regarding safety to the SO. Oftentimes, the pediatrician will not be deployed directly into any search and rescue efforts and will

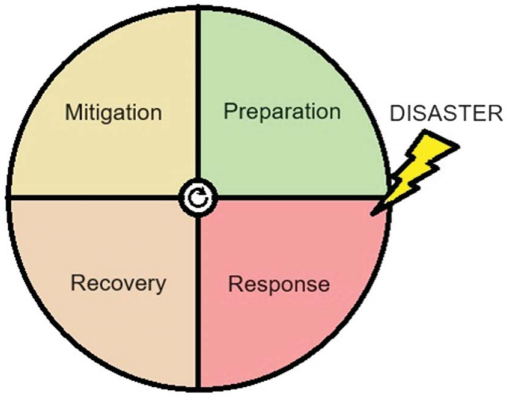


FIGURE 1. The disaster cycle. Planning for a disaster to occur is done during the preparation phase. The initial reactive steps that occur once disaster strikes occur during the response phase. The recovery phase involves the steps that are taken to establish a new normal state, with better preparedness for future disasters and increased community resilience. Mitigation involves learning from previous disasters to prevent or limit the impact of future disasters. Image based on Klein et al.[23,38,39]

instead be stationed nearby to provide medical care for victims who self-present or are rescued. In many disaster response situations, a pediatrician may be called on to care for both child and adult disaster survivors.

The next step is to triage victims of the disaster. Various models for how to quickly triage patients in a mass casualty incident exist, such as the Simple Triage and Rapid Treatment system (START/JumpSTART, Figure 2), in which patients are tagged green (the "walking well"), yellow (significantly injured and requiring urgent medical attention), red (patients with life- or limb-threatening injuries requiring emergent attention), or black (cardiac arrest or deceased).[23] Any critically ill children will need to be rapidly assessed and stabilized. A plan should be made for identifying any unidentified children and to reunify them with parents or other family when possible (see Initial Aftermath section). At the very least, a plan needs to be enacted for how to communicate with family members regarding the safety of their children.

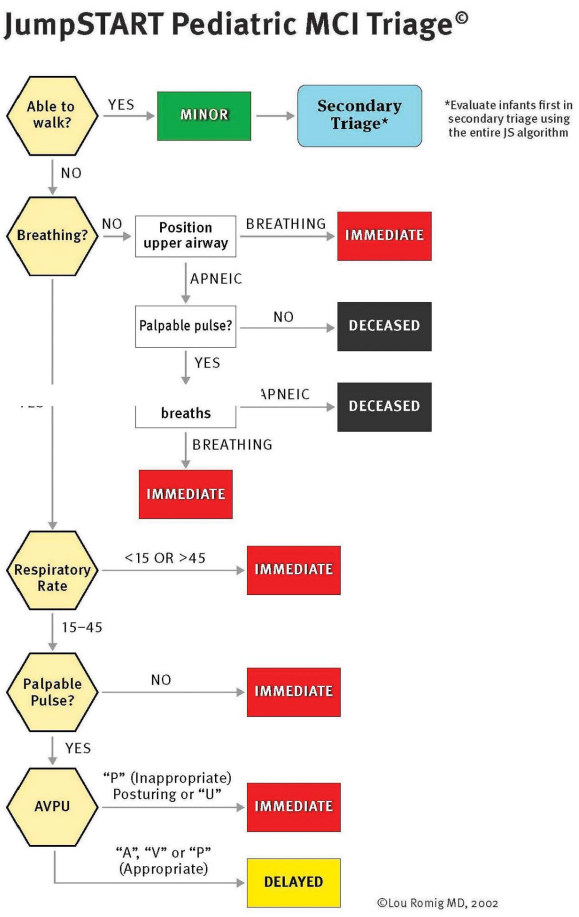


FIGURE 2. JumpSTART triage tool. The JumpSTART triage algorithm provides a rapid way to prioritize which victims of a natural disaster need immediate medical attention. Courtesy of Lou E. Romig MD, FAAP, FACEP. AVPU (Neurologic Assessment): A, Alert; V, Responds to verbal stimuli; P, Responds to painful stimuli; U, Unresponsive to noxious stimuli.
Abbreviation: JumpSTART, Simple Triage and Rapid Treatment.

Initial Aftermath

In the immediate aftermath of a natural disaster, efforts should be made to ensure access to clean water, food, and shelter while simultaneously working to reunite children with their families. Ideally, infection prevention measures should be enacted to reduce the likelihood of disease outbreaks.

One challenge that responders often face is identifying pediatric patients and contacting their parents or family members. For example, after Hurricanes Katrina and Rita, the National Center for Missing and Exploited Children received more than 34 000 calls. Reunification describes efforts made to voluntarily return children to their family or another trusted guardian after they have been separated.[24]

Federal Emergency Management Agency (FEMA) has prepared a guide to help reunify children after disasters. Table 2 provides strategies for identifying family members.

Of note, some pitfalls of which the pediatrician should be aware include the following:

- Trafficked, exploited, or runaway children may not accurately self-identify.
- Unaccompanied children are at risk for exploitation; therefore, only authorized persons should be permitted access to sheltered children.

Children requiring additional assistance or who have barriers to communication may require appropriately trained staff.[25]

Previous work has demonstrated that when a disaster occurs during school hours, 63% of parents and guardians

TABLE 2. Strategies to Aid in Identifying a Child or Parent During a Natural Disaster

Strategies for Identifying Children and Their Parents
Digital images and/or videos
Preexisting identification
Identifying marks, scars, etc
Identifying or tracking bracelets applied in the prehospital setting
Fingerprint databases
Government-issued identification
Safe words
Accessing data from location-based apps

Abbreviation: app, application.

would go directly to a child's school to reunify with their children despite receiving direct orders to evacuate.[25]

Common practices within the disaster response include conducting a needs assessment, incorporating local medical staff into the disaster response, implementing a clear chain of command, and ensuring that patients and medical staff have sufficient access to food and clean water throughout the disaster response. Larger-scale events require a plan for integrated, efficient response without convergent volunteerism, especially when there is external or even international response; such well-intentioned response can quickly exhaust local resources and add additional victims.

Recovery

The pediatrician should monitor patients for delayed health effects and psychologic trauma, including depression and acute stress disorder. In young children, depression can present with regression, clinginess, withdrawal, crying, and somatic symptoms, such as abdominal pain. Older children may present with similar symptoms and acting out. In addition to these symptoms, adolescents may present with suicidal ideation and self-harm. Delayed presentation of posttraumatic stress disorder is also possible. The pediatrician should work with local mental health services to connect children and their families with counseling as needed.

Children with preexisting chronic health conditions or disabilities will often need extra attention to ensure that they have access to essential medications and equipment. Pediatricians may need to coordinate with local authorities to source these items.

Pediatricians should be prepared to help children who were physically injured during the disaster to access subspecialty care when needed, as well as physical therapy and rehabilitation.

Pediatricians may engage with schools and community organizations to help facilitate community-based interventions that promote recovery and foster resilience. Likewise, pediatricians can help advise local authorities and community outreach agencies how to support vulnerable children within the community who may be disproportionately impacted due to social determinants of health.

PREPARATION AND MITIGATION

One way that pediatricians can help prepare their patients and communities for a disaster is to engage in community preparedness initiatives and to develop a disaster response plan, particularly if their community is known to be more susceptible to specific types of disasters, such as hurricanes, floods, or wildfires. In these cases, pediatricians can provide anticipatory guidance to parents and children during well-child visits regarding topics such as the importance of having an emergency evacuation plan and emergency kits, a reunification plan, and how to enroll in local alert systems. For suggested contents of an emergency kit, please see Table 3. Teaching children how to recognize a possible impending emergency and seek shelter or help increases the likelihood of positive outcomes in disasters. Likewise, pediatricians can help families with children who have specific needs with advance preparedness, such as an awareness of local generator programs for children who use mechanical ventilation.

Pediatricians should consider having parents and guardians sign waivers during well-child visits, so that in the event of a disaster, emergency consent for treatment is already in place. An example waiver, from the FEMA guidelines for the Post-Disaster Reunification of Children, is below:

> "In the event of an emergency requiring medical treatment, I, [parent's name], hereby grant permission for all medical and/or dental attention to be administered to my child/children, in the event of an accidental injury

TABLE 3. Suggested Contents of an Emergency Response Kit

Nourishment	Medical Supplies	Sanitation Supplies	Safety Items	Shelter Items
Potable water (1 gallon per person per day)	Nonprescription medications	Diapers and wipes	Flashlight	Extra clothes, socks, and undergarments
Nonperishable food	Durable medical equipment (orthotics, glasses, hearing aids, etc)	Menstrual products	List of emergency contacts	Transition objects
Pet food, if applicable	Photocopy of identification and medical insurance card	N95 and/or face masks	Battery-powered radio; extra batteries	Blankets or coats
Water purification tablets	First aid kit	Waterproof matches	Multipurpose tool	Games and activities for kids
			Cellphone; chargers	Rain and/or snow gear
			Whistle	

Pediatricians can provide anticipatory guidance regarding what essential supplies parents should maintain as part of their emergency readiness plan based on what types of natural disasters are most likely to be prevalent in their area of practice.

or illness, until such time as I can be contacted. This permission includes, but is not limited to, the administration of first aid, the use of an ambulance, and the administration of anesthesia and/or surgery, under the recommendation of qualified medical personnel."[26]

Pediatricians should consider ways to ensure that medical records of patients within their panel can be rapidly accessed by emergency personnel in the event of an emergency.[24]

There are many ways that pediatricians can become more knowledgeable about disaster preparedness. Additional training is available through FEMA (https://www.fema.gov) and can be accessed through the agency website. Pediatricians asked to respond during the acute phase of a natural disaster should be familiar with the National Incident Management System (NIMS) (https://www.fema.gov/emergency-managers/nims). Pediatricians should ensure that the facilities in which they practice have plans to operate in the event of problems such as water damage or power interruption. Such plans include redundancy for patient health care information, business financial services, and predesignated alternate care sites.

Pediatricians can serve as powerful community advocates. Pediatricians can invite those who are most at risk or have social factors contributing to their vulnerability to community meetings about disaster planning to ensure that they have a voice in the development of plans for a disaster response (Table 4). For example, the parents of children who use wheelchairs should be encouraged to meet with school authorities to help plan evacuation routes for children in a fire.

TABLE 4. Factors Contributing to Disaster Vulnerability and Resiliency

Promoters of Resiliency
Strong social support networks
Strong Family Cohesion
Effective local leadership and planning
Access to health care
Education and preparedness training
Community engagement
Economic stability
Promoters of Vulnerability
Limited social support
Poor infrastructure
Economic disadvantage
Developmental disability
Dependency
Communication and comprehension limitations
Limited mobility
Pre-existing mental and physical health conditions
Technology dependence
Lack of access to health care

Table based on Peek,[35] Paton and Johnson,[36] and Mohammadinia et al.[37]

CASE STUDY: HURRICANE MARIA, SEPTEMBER 2017

Hurricane Maria, a Category 5 hurricane, tore through Puerto Rico and the Caribbean in September 2017. An estimated 3059 people died due to the hurricane, and its lasting impact continues to be felt even today.[27]

One of the most important takeaways from Hurricane Maria is how a lack of adequate preparation and infrastructure set the stage for catastrophic devastation. As an additional precipitating factor, the island had not recovered from Hurricane Irma, which made landfall on September 6, 2017, only 14 days before Maria struck on September 20. Nearly the entire island lost power, so radar, weather stations, and cell service were all disrupted, which complicated efforts to assess the emergent need for assistance. Wind gusts, rainfall, flash flooding, and landslides caused 97% of the island's roadways to become impassable during and immediately after the storm.[28]

Given that Puerto Rico is an American territory, not a state, and its residents are US citizens, significant criticism has brought to light the disparities in how the US response to Maria was hampered by institutionalized inequity, and the federal government released a 936-page report contrasting the differences in response to Hurricanes Harvey (in Houston, Texas) and Maria, as well as highlighting how in both disasters, those who are living in poverty, people who are racially minoritized, those with disabilities, and people who are lesbian, gay, bisexual, and transgender had worse access to assistance and outcomes.[29] These data serve as an important, evidence-based reminder that pediatricians should target their response efforts to specifically reach children who may otherwise be at risk of marginalization.

Regarding how physicians were able to care for the local population during and after the storm, one can look to the example set by the Southwestern Regional Academic Medical Center. Before landfall, preparations were made so that resident physicians and faculty teams were created that could remain in the hospital for at least 3 days. The hospital provided food and places for the staff to sleep. Some of the residents were permitted to bring close family members to the hospital so that physicians could work knowing that their children were safe. Elective surgical cases were canceled, and medical residents were tasked with caring for patients with the highest need, such as in the EDs and intensive care units. Efforts were also made to minimize

TABLE 5. Key Takeaways Learned by Residency Program Leadership at Southwestern Regional Academic Medical Center in the Aftermath of Hurricane Maria

Maintain open communication and include medical residents in daily meetings to assess the status of the hospital because the residents were also on the frontlines with faculty.
Consider all possible ways to communicate, including live messengers, satellite phones, and social media platforms.
Establish redundant means of communication in the event of outages and disruption.
Consider educational interventions, such as moving examination dates, and be proactive about reaching out in advance to the appropriate entity when indicated.
Ensure there is enough food and water available for medical staff, including medical residents, to last at least 2 weeks.
Empty the hospital as much as possible in anticipation of an influx of new patients in the immediate aftermath of a disaster. Discharge patients who can safely leave the hospital. Cancel outpatient appointments and surgeries.
Conduct routine disaster drills.
Ask for help from local institutions when possible.
Pay the staff in cash, if possible, in the event of power outages, so that they can purchase gasoline and food to be able to commute back and forth to the hospital.
Watch for signs of burnout and caregiver stress, particularly in trainees.
Have access to essential supplies that do not require electricity to function, including paper health records, physical textbooks and other hard copies of key information, blackboards for teaching, bicycles, flashlights, gas stoves, etc.

disruption in education for medical residents during hurricane season. For example, program directors successfully advocated for the American Board of Family Medicine to change the date of the in-training examination to December in future years. Satellite telephones were made available for future disasters, and landlines were reestablished because they do not require electricity to operate, unlike cell phones.[29] Key takeaways for the medical residents and program leadership regarding hurricane preparation and response are summarized in Table 5. Program leadership developed these recommendations in preparation for future hurricanes.[29]

In the initial recovery phase, millions of people were left without electricity. Ninety-five percent of Puerto Rico did not have electricity or cell service; half of people had been left without water service. These statistics remained relatively unchanged for weeks. Electricity was not fully restored to the island until 11 months after the hurricane struck, creating the longest blackout in American history.[30,31]

It is important to note that many children who experienced Hurricane Maria firsthand ultimately were displaced, and approximately 42 000 children fled Puerto Rico with their families. Therefore, pediatricians across the country assumed care of Maria survivors. Half of Puerto Rican public schools did not reopen 2 months after the disaster, and hundreds remained closed a year after the hurricane.[32–34] Many teachers had likewise relocated from the island. The remaining police officers were pulled to help with securing supplies and therefore were unavailable for families facing crises such as intimate partner violence. Five of the 7 shelters for women and children closed.[32] The resulting huge disruptions in social networks and societal safety nets underscore a need for ongoing trauma-informed care for children and their families.

CLINICAL PEARLS

- Understand the specific disaster risks in your community and educate families on preparedness, including evacuation plans and emergency kits.
- Be vigilant in identifying physical and psychologic impacts on children after disaster, providing immediate care and long-term support. Use available resources for mental health support, and ensure continuity of care for those with chronic health issues.
- Advocate for and participate in efforts to secure food and nutritional support for affected families.
- Actively engage in community preparedness initiatives and advocate for comprehensive disaster response plans that consider pediatric needs.
- Seek additional training in disaster preparedness and response, familiarize yourself with the NIMS, and ensure your practice is prepared for infrastructure challenges.
- Recognize that children from marginalized or low-income families may face greater barriers to recovery and require additional support and advocacy to access health care, safe housing, and social services.

Pediatricians play a pivotal role in disaster preparedness, response, and recovery, with a focus on addressing the unique needs of children. By incorporating these clinical pearls into practice, pediatricians can contribute significantly to the resilience and recovery of the pediatric population after natural disasters.

Summary

- Natural disasters pose significant challenges to the well-being of children, affecting both their physical and mental health. Pediatricians should be aware of injury patterns, illnesses, and mental illness seen in the aftermath of various natural disasters.[1,2,5,11,14,35] (Based on strong research evidence and consensus).

- Pediatricians play a vital role in disaster response, necessitating an understanding of local disaster risks and active participation in prevention and mitigation.[1,20,25] (Based on some evidence and consensus).
- Effective disaster management requires a multidisciplinary approach to ensure protection of a young, vulnerable population.[15,24,25] (Based on some evidence and consensus).



Take the quiz! Scan this QR code to take the quiz, access the references, and view and save images and tables (available April 1, 2025).

PIR QUIZ

1. A pediatrician is providing medical care at a center after the community experienced a tornado. Volunteers at the center receive training on how to triage children in the initial aftermath of the tornado using the JumpSTART Pediatric Mass Casualty Incident Triage workflow. The first step in the decision tree for this workflow is to assess the child's what?

   A. Ability to walk
   B. Heart rate
   C. Level of alertness
   D. Respiratory rate
   E. Response to pain

2. A pediatrician, who lives in a community that frequently experiences hurricanes, has a 10-year-old patient who uses a wheelchair for mobility. At a well-child visit, the pediatrician is most likely to provide the child's family with which of the following recommendations regarding the care of their child?

   A. Avoid keeping cash at home and use only credit cards
   B. Avoid the topic of hurricanes to minimize trauma
   C. Focus on obtaining swimming lessons
   D. Move to another part of the state without hurricane risk
   E. Place a signed consent for emergency care in the child's medical record

3. A physician leader in a multisite clinic system is asked to develop an emergency preparation program for the health system. The physician would likely use which of the following systems to organize their emergency preparedness plan?

   A. National Incident Management System
   B. National Incident-Based Reporting System
   C. National Notifiable Diseases Surveillance System
   D. National Outbreak Reporting System
   E. National Healthcare Safety Network

4. A pediatrician in an area with frequent floods volunteers to support disaster readiness in the community. The community has volunteers from various professions. From the tasks below, the pediatrician is uniquely positioned to be assigned to which of the following tasks for preparation?

   A. Focus group to identify vulnerable populations
   B. Intubation training in the emergency department
   C. Managing emergency communication access
   D. Sorting food at the local food bank
   E. Training crews to fill sandbags

5. Residency program directors meet at a national meeting to discuss emergency preparedness in the context of their training programs. They will likely include which of the following strategies as part of the recommended planning?

   A. Avoid involving residents with emergency planning details
   B. Encourage residents to challenge a chain of command hierarchy in a disaster
   C. Place pediatric residents in schools before the emergency event
   D. Prepare a resident team to be in the hospital for 3 days in a disaster
   E. Send all residents home before severe weather events

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2025 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2027, however, credit will be recorded in the year in which the learner completes the quiz.



2025 *Pediatrics in Review* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *Pediatrics in Review* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2025. To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.

Food Introduction in Infancy

Cleavon Covington, MD, MS,[1,2] Fiona Adame, DO,[1,2] Joanne Acevedo, MD,[1,2] Meredith Suggs, MD[1]

[1]Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas
[2]Division of Allergy and Immunology, University of Texas Medical Branch, Galveston, Texas

PRACTICE GAP

Despite an abundance of information available regarding pediatric food introduction, significant discrepancies exist in providers' guidance to parents on the optimal timing, types, and methods of introducing solid foods to infants. Addressing this education gap is essential for ensuring healthy introduction of complementary foods, mitigating the rising incidence of food allergies, and preventing feeding challenges in infants overall.

OBJECTIVES *After completing this article, readers should be able to:*

1. Appropriately guide parents of atopic/nonatopic infants on the introduction of allergenic foods
2. Describe the risk and benefits of early introduction
3. Provide guidance to parents regarding introduction of complementary foods
4. List the protective benefits of breastfeeding for food allergy development

AUTHOR DISCLOSURE: Drs Covington, Adame, Acevedo, and Suggs have disclosed no financial relationships relevant to this article. This review does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAAAI	American Academy of Allergy, Asthma, and Immunology
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACAAI	American College of Allergy, Asthma, and Immunology
ACOG	American College of Obstetrics and Gynecology
CSACI	Canadian Society of Allergy and Clinical Immunology
EAT	Enquiring About Tolerance
FALCPA	Food Allergen Labeling and Consumer Protection Act
FASTER	Food Allergy Safety, Treatment, Education, and Research
IgE	immunoglobulin E
LEAP	Learning Early About Peanut Allergy
NIAID-AG	National Institute of Allergy and Infectious Diseases-Addendum Guidelines
PETIT	Prevention of Egg Allergy with Tiny Amount Intake Trial
WHO	World Health Organization

INTRODUCTION

The introduction of solid foods to infants marks a significant milestone in their development, yet introducing solid foods can also be a source of confusion and concern for parents and caregivers. With overwhelming information available, navigating the infant feeding landscape can be intimidating. In recent years, a growing body of research has shed light on optimal practices for introducing solid foods to infants. This research offers invaluable insights for parents seeking to provide the best nutrition for their children. Nevertheless, increased awareness about food allergies has also led to increased anxiety among parents regarding the introduction of new foods to their infants. Close to 6% of children in the United States have food allergies,[1] which has an annual cost of $24.8 billion.[2] The most prevalent food allergies in children include peanut, egg, and cow's milk.[2] This review article consolidates recommendations by presenting the current evidence surrounding infant food introduction. Key topics addressed include the optimal timing and methods for introducing solid foods, strategies for safely introducing potentially allergenic foods, and special considerations for children with atopic conditions such as atopic dermatitis and food allergies. This review seeks to provide health care professionals and caregivers the knowledge to make informed decisions on food introduction and mitigate the risk of adverse reactions in infants and children.

TABLE 1. Summary of Food Introduction Recommendations

Food	Recommended Introduction Timeline	Quantity and Types of Food	Frequency of Ingestion	Quality of Evidence
Egg	**All infants:** 4–11 mos[9,12]	**Fully heated/baked eggs:** • ¼ Muffins, low-sugar cookies,[12] cake[12,25] • Store-bought items: egg in bottom half of ingredients[25] • Unlimited precautionary label[25] **Partially heated egg:** • 1–2 teaspoons scrambled, boiled, egg noodles[25] • ¼ French toast,[25] snack cakes[25]	Ideally daily, but at least weekly[12,25]	Level A for timeline, Level D for quantity and frequency
Peanut	**All infants:** 4–11 mos[9,12] **Eczema:** 4–6 mos[19]	2 g of peanut protein (~2 teaspoons)[12] • Peanut powder mixed with milk or fruit[12] • Smooth diluted peanut butter[12] (~2/3 bag) • Peanut butter snacks (ie, Bambas)[12]	Three times per week[12]	Level A
Cow's milk	**All infants:** 4–11 mos[20]	**Exclusively breastfed:** Fully cooked milk: • ¼ Muffins, low-sugar cookies,[12] cake[12] Yogurt, cheese, custards (2–4 oz)[20] **Commercial formula fed:** Unlimited **All infants:** Whole liquid cow's milk after 1 y[5]	Twice weekly[12]	Level D [low quality of evidence]
Wheat/gluten	**All infants:** 4–11 mos[7,9,12]	2 g wheat protein[12] Soft, cooked pasta,[12] bread,[12] baked goods,[12] cereal[7]	Twice weekly[12]	Level D [low quality of evidence]
Tree nut	**All infants:** 6–11 mos[12]	2 g tree nut protein[12] Tree nut butters[12]	Twice weekly[12]	Level C for timeline, Level D for quantity and frequency
Sesame	**All infants:** 6–11 mos[12]	2 g of sesame protein[12] Hummus or tahini[12]	Twice weekly[12]	Level C for timeline, Level D for quantity and frequency
Fish	**All infants:** 6–11 mos[12]	At least 2 g of fish protein but no more than 2 age-appropriate servings[12]	Twice weekly[12]	Level C for timeline, Level D for quantity and frequency
Shellfish	**All infants:** 6–11 mos[12]	2 g of shellfish protein	Twice weekly[12]	Level C for timeline, Level D for quantity and frequency

INTRODUCTION OF GENERAL COMPLEMENTARY FOODS

Complementary feeding refers to introducing foods alongside human breast milk or commercial formula to meet the nutritional needs of infants as they grow beyond age 6 months.[3] This transition from exclusive milk feeding to a diverse diet is crucial for the infant's optimal growth and social, emotional, and cognitive development.[3] In this section, we will discuss the timing, selection of foods, preparation methods, progression of the diet, and possible risks of complementary food introduction based on current data and recommendations.

Timing

The timing of introducing complementary foods is a critical factor in infant nutrition.[4,5] Exclusive breastfeeding through the first 6 months of life has been recommended by the World Health Organization (WHO) since 2002.[3,4] The American Academy of Pediatrics (AAP),[3] American College of Obstetrics and Gynecology (ACOG), and the American Academy of Family Physicians (AAFP) all also recommend initiating complementary foods around age 6 months, while avoiding introduction before 4 months.[4] The AAP also advocates that breastfeeding can be continued beyond age 2 years if desired by both the mother and infant.[3] Delaying the introduction of complementary foods beyond 6 months may lead to nutritional deficiencies[5,6]; although currently controversial, there is a chance that introducing solids too early may increase the risk of obesity.[4–6]

Selection

Organizations such as the US Department of Agriculture and the WHO recommend incorporating foods rich in macronutrients such as protein, fats, and carbohydrates and micronutrients such as iron, zinc, calcium, and vitamins A, B, C, and D while discouraging the inclusion of caffeine, added sugars, and high-sodium foods.[3,5,7]

Common first foods include the following:

- Iron-rich foods: Experts recommend that infants receive a daily intake of iron-rich foods in the form of iron-fortified cereals, red meat, fish, poultry, legumes, and nuts.[5–7]
- Pureed fruits and vegetables: The addition of pureed or mashed fruits and cooked vegetables such as bananas, leafy greens, squash, potatoes, carrots, and peas are excellent sources of vitamin A, vitamin C, B vitamins, and calcium.[7]
- Protein-rich foods: Cooked and pureed meats, poultry, fish, eggs, grains, nuts, and legumes provide essential protein, iron, and zinc.[7]

Advancing the Diet

Because iron stores become depleted by age 4 to 6 months, iron-fortified cereals and pureed meats are important complementary foods to first introduce to breastfed infants.[8] Despite the common practice of pediatricians recommending the introduction of iron-fortified cereals and vegetables before fruits to avoid exposure to sweeter flavors, there is no evidence to support any particular order of solid food introduction.[8] The WHO suggests gradually introducing various food textures and consistencies, beginning with pureed and mashed foods before advancing to more solid options, aiming for children to partake in family meals by approximately age 1 year.[6] Additionally, it is recommended to introduce foods with lumpy textures, such as finger foods, between ages 8 and 10 months, because delaying beyond this timeframe has been linked to pickiness and food refusal behaviors.[6,7] When introducing solids, caution must be taken with foods that can be choking hazards, such as raw fruits and vegetables (grapes and carrots) and nuts.[7] Parents should emphasize caution in ensuring that the consistency of the food is adequate for the child, such as using purees or cutting food into smaller pieces.[7] Furthermore, the child should have adequate head control to sit in a feeding chair and be eager to consume foods.

POSSIBLE RISKS OF EARLY INTRODUCTION

The early introduction of solids has been associated with potential risks and benefits, particularly concerning allergies, obesity, and the intestinal microbiome.[4,9]

- Allergies: Although early introduction was once thought to increase allergy risk, recent evidence suggests early introduction may decrease the likelihood of developing food allergies.[4] Two studies, Learning Early About Peanut Allergy (LEAP) and Enquiring About Tolerance (EAT), demonstrate lower allergy rates in infants exposed to allergenic foods before age 6 months, highlighting a potential opportunity to achieve oral tolerance with early introduction.[4]
- Obesity: The evidence is limited that introducing solids before age 6 months increases the risk of obesity.[4] Although most studies found no association between early introduction and future obesity, some observational studies hint at a potential link, although this could be influenced by factors such as rapid weight gain rather than early solid introduction.[4,9]
- Intestinal microbiome: The introduction of solids alters the infant's intestinal microbiome, increasing diversity and shifting bacterial populations.[4] Some association has been found tying low intestinal microbial diversity during infancy to a risk for developing conditions such as colic, eczema, asthma, and type 1 diabetes in the future.[4]

INTRODUCTION OF ALLERGENIC COMPLEMENTARY FOODS

The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) and the Food Allergy Safety, Treatment, Education, and Research (FASTER) Act, pivotal in the field of food allergies, have identified major food allergens. FALCPA, for instance, recognized peanuts, cow's milk, egg, wheat, soy, tree nuts, fish, and crustacean shellfish as the common food groups that make up most food allergies (Table 1).[10] The FASTER Act, on the other hand, identified sesame as a major food allergen in the United States, with labeling requirements taking effect on January 1, 2023.[10] It is worth noting that egg and cow's milk are the most common allergens in infancy.[11]

Breastfeeding

According to the 2013 American Academy of Allergy, Asthma, and Immunology (AAAAI), Canadian Society of Allergy and Clinical Immunology (CSACI), and the 2019 AAP Clinical Report, if a child is diagnosed with a food allergy and is exclusively breastfeeding, the mother does not have to exclude these foods from her diet.[12] Another study showed that breastfeeding infants had a lower risk of developing wheat allergy if introduction occurred while they were still being breastfed.[12] A study in Canada showed that if peanuts were introduced to breastfeeding infants via breastmilk from a peanut-consuming breastfeeding mother and then having direct oral ingestion of peanuts prior to age 1 year, such introduction was protective against peanut sensitization until at least age 7 years.[13] The AAAAI, American College of Allergy, Asthma, and Immunology (ACAAI), and CSACI also wrote a consensus report that some research indicates that concurrent breastfeeding and allergen

introduction can potentially protect against the onset of food allergies.[12] However, there are still some conflicting data on this benefit, and the duration of breastfeeding as a contributing factor remains unresolved.[12] The WHO conducted a systemic review, comparing exclusive breastfeeding until age 6 months vs 3 to 4 months.[14] The benefits of exclusive breastfeeding were lowering the risk of gastrointestinal illnesses in children and quicker weight loss for mothers. However, there are no data suggesting that it will reduce the risk of allergies.[14]

Early Introduction

Based on studies showing benefits, there has been a switch in the recommendations for the early introduction of allergenic foods. The United Kingdom–based trial mentioned earlier, LEAP, showed that introducing peanuts prior to age 1 year decreases the likelihood of developing a food allergy to peanuts in high-risk infants.[15] An Australian study, EarlyNuts, showed that the rate of early introduction of peanuts increased from 28.4% to 88.6% after an update to the infant feeding guidelines in 2016 following the LEAP study.[16]

The National Institute of Allergy and Infectious Diseases-Addendum Guidelines (NIAID-AG) recommend consuming safe peanut powders/flours and snacks such as peanut puffs (Bamba or Cheeky Monkey) on an average of 2 g of peanut protein (~2 teaspoons) 3 times a week to maintain tolerance.[12] The peanut protein powder can be mixed into breast milk or formula, or with pureed foods.[12] The Prevention of Egg Allergy with Tiny Amount Intake Trial (PETIT) in Japan showed a protective effect when infants consumed 50 to 250 mg of cooked egg daily between ages 6 and 12 months.[12] Fully cooked/baked eggs (ie, muffins) are heated to at least 350 °F for at least 30 minutes.[17] The recommendation is that fully cooked/baked eggs should be introduced first, compared with raw or undercooked eggs, as nonbaked eggs have a higher likelihood of triggering an allergic reaction.[12] Sesame and tree nuts can be introduced in pureed or paste-type foods to avoid choking hazards, also around age 6 months, once the infant has tolerated typical complementary food introduction.[12] The overall goal is regular exposure to allergenic foods throughout the years to maintain tolerance, as there is no good consensus regarding the specific protein amount or interval of ingestion.[12]

Timeline

The recommended age for introduction of specific complementary allergenic foods is varied. Soriano et al reviewed the available evidence and found that peanut and egg introduction *should* occur between ages 4 and 11 months to lessen the likelihood of developing a food allergy.[9] Scarpone et al found evidence showing that introduction at age 3 to 6 months had a 40% reduction of egg allergy development, whereas introduction at age 3 to 10 months had a 69% reduction of peanut allergy.[18] Roberts and colleagues developed a model for the burden of peanut allergy across an entire population using data from the LEAP, EAT, and other pivotal trials.[19] The model revealed that a 77% reduction in the burden of peanut allergy can be achieved if peanut is introduced to high-risk infants with any eczema severity at age 4 months and in all other infants at age 6 months.[19]

The evidence for when to introduce cow's milk into the diet for allergy prevention shows low certainty,[9,18] but whole liquid cow's milk should be delayed until age 1 year due to adverse health effects, particularly iron deficiency anemia.[5] Other forms of cow's milk, such as yogurt, cheese, custards, and commercial formula, can be introduced before age 1 year.[20] Hydrolyzed formula is not recommended as a means for food allergy prevention.[12] The evidence shows low certainty regarding the timing of the introduction of wheat/gluten into the diet and its relationship with wheat allergy.[9,18] However, there is some high-certainty evidence showing that early introduction did not have an increased risk for developing celiac disease.[9]

The first introduction of a food should be performed at home vs a clinical environment, but it is acceptable to introduce under clinical supervision if there is a risk that, due to parental fear, there will be unnecessary avoidance of the food.[12] It has been common to recommend introducing 1 complementary new food every 3 days to see if reaction occurs, although data do not support this method.[12] Acidic fruits commonly cause a contact irritation reaction that can be mistaken for an immunoglobulin E (IgE)–mediated reaction, which can cause further delayed introduction of the food.[12] However, contact dermatitis does not carry the risk of progression to anaphylaxis and is often self-limited, so delayed introduction for this reason is not recommended.[12] Nonallergenic complementary foods should be introduced first to assess tolerance of solid foods and to prevent intolerance from being mistaken for an allergic reaction.[12]

INTRODUCTION OF FOODS TO PATIENTS WITH ATOPY

The topic of introducing foods, particularly those that are potentially allergenic, to patients with existing atopic conditions has been evolving. Since the publication of the LEAP trial in 2015,[15] many of the guidelines published by professional societies around the world have focused on guiding parents and practitioners on introducing peanuts. As mentioned

above, most of these guidelines need to be supported by sufficient evidence regarding the timing of introducing other significant allergens. Also, these guidelines vary in how they define infants at higher risk and whom and when to test before food introduction. In response, the AAAAI, ACAAI, and CSACI provided an extensive review of evidence and formulated a consensus statement in 2020 to address how to define an infant as high risk for the development of food allergy, the timing of introduction of potentially allergenic foods to these patients, and when to refer to an allergist for possible testing or supervised oral food challenge.[12]

Defining High-Risk Infants

There is no international consensus on defining a high-risk infant for developing food allergy. The LEAP and EAT studies set the current standard for high-risk patients: severe eczema and sensitization to egg allergy or other food.[21] The NIAID-AG include mild to moderate eczema as a high-risk factor, and previous guidelines include having a first-degree relative with atopy as a risk factor; however, some considered this too inclusive.[12] To help clinical decision-making, a 2021 AAAAI/ACAAI/CSACI consensus report proposed a risk gradient for the development of food allergy to help clinicians risk-strategize their patients.[12] The infants at highest risk are those with severe eczema, followed by those with other food allergies, followed by those with mild to moderate eczema, followed by those with a family history of atopy.[12] Therefore, for the purpose of this article, we are defining high-risk infants as those with eczema, asthma, other food allergies, and a family history of atopic diseases.

Timing of Introduction to High-Risk Infants

The AAAAI/ACAAI/CSACI workgroup reviewed 7 randomized control trials that investigated the relationship between the timing of the introduction of peanuts and eggs and the development or prevention of food allergy in both standard-risk and high-risk patients.[12] They concluded that peanut and egg allergens should both be introduced between ages 4 and 6 months for all infants.[12] There are less data surrounding the timing of introducing other food allergens and the impact on the development of food allergies; however, current observational studies suggest there is no harm in early introduction of these allergens other than the potential harm in delaying introduction.[12] It is important to emphasize to patients that regular, continued consumption of the food is essential to maintaining tolerance once the food is introduced.[12]

Testing Prior to Introduction

The guidelines for allergy testing prior to food introduction have been continually evolving. After the LEAP study 2015, the recommendation was to test before introducing peanuts to those infants they defined as high-risk.[22] The British Society of Allergy and Clinical Immunology 2018 recommended peanut introduction at age 4 months without risk stratification or testing for all infants.[23] After a review of the evidence, the AAAAI/ACAAI/CSACI consensus statement in 2021 concludes that for both standard and high-risk infants, skin or serum IgE testing is not required prior to the early introduction of peanut or egg.[12] However, screening should remain an option for families who want to test before the introduction rather than delaying the introduction, which could cause more harm.[12] Overall, the current stance is that there is no evidence to support preemptive allergy testing prior to introduction of allergenic foods due to the risk of getting false positives, the low-cost-effectiveness, and the low risk of a severe reaction on first exposure.[24]

Summary

- Exclusive breastfeeding is recommended through the first 6 months of life (WHO, ACOG, AAP, and AAFP),[3,4] and the AAP advocates that breastfeeding can be continued beyond age 2 years if both the mother and infant desire.[3] (Level A; Strong Recommendation, based on clinical studies)
- Complementary foods should be rich in macronutrients such as protein, fats, and carbohydrates and micronutrients such as iron, zinc, calcium, and vitamins A, B, C, and D.[3,5,7] These foods should be absent of or have minimal amounts of caffeine, added sugars, and high-sodium content.[3,5,7] (Level A; Strong Recommendation, based on clinical studies)
- The LEAP study showed that introducing peanuts before age 1 year decreases the likelihood of developing a food allergy to peanuts in high-risk infants.[13] (Level A, Strong Recommendation, based on clinical studies)
- The PETIT study showed a protective effect when infants consumed cooked eggs daily between the ages of 6 and 12 months.[12] (Level A, Strong Recommendation, based on clinical studies)
- There is evidence that liquid cow's milk should not be introduced until after age 1 year for the risk of iron deficiency anemia, but families may introduce nonliquid cow's milk prior to this age.[5,9,18,20] (Level A, Strong Recommendation, based on clinical studies)
- The evidence shows low certainty on the timing of the introduction of wheat/gluten into the diet and

its relationship with wheat allergy.[9,18] (Level C, based on observational studies and inconsistent study findings)

- An AAAAI/ACAAI/CSACI consensus report proposed that severe eczema is the highest risk factor for an infant developing a food allergy.[12] (Level B, based on clinical and observational studies)
- There is no evidence to support preemptive allergy testing prior to introducing allergenic foods due to the risk of getting false positives, the low-cost-effectiveness, and the low risk of a severe reaction on first exposure.[24] (Level C, based on observational studies and inconsistent study findings)
- The overall goal is regular and maintained exposure to allergenic foods throughout the years to maintain tolerance.[1] (Level C, based on observational studies and inconsistent study findings)

Take the quiz! Scan this QR code to take the quiz, access the references, and view and save images and tables (available April 1, 2025).

PIR QUIZ

1. The mother of a former 32-week premature infant, now aged 5 months, is frustrated by the conflicting recommendations she has received regarding the best time to introduce complementary solid foods into her child's diet. She does not know whether to use their corrected or uncorrected age to start solid food. A minimum ability to perform which of the following tasks should an infant demonstrate before safely initiating this next feeding step?

   A. Hold a cup securely with one hand
   B. Maintain head control while sitting in a feeding chair
   C. Pick up small pieces of food from a tray with their fingers
   D. Sit independently in a feeding chair
   E. Use their index finger to point to a desired food

2. During a presentation to expectant parents, you are asked by the expectant parents why the current recommendations regarding complementary food introduction are so different from the ones they grew up with and from what they keep hearing from their own parents. You explain that the early introduction of complementary foods is thought to decrease the likelihood of a child developing which of the following conditions?

   A. Celiac disease
   B. Food allergies
   C. Nutritional deficiencies
   D. Obesity
   E. Type I diabetes mellitus

3. The mother of a 4-month-old infant wants to discuss the best possible ways to prevent food allergies in her child. She is currently exclusively breastfeeding. Based on this information, which of the following dietary strategies would you recommend as her next best step to achieve this goal?

   A. Continue breastfeeding and begin introducing small amounts of solid food products on a regular basis
   B. Continue breastfeeding but eliminate allergenic foods from mother's diet
   C. Continue exclusively breastfeeding and do not start complementary feedings
   D. Discontinue breastfeeding and switch to a hydrolyzed formula for feeding
   E. Discontinue breastfeeding and switch to whole milk for feeding

4. During a postclinic conference with a group of medical students, you are reviewing optimal practices for the introduction of complementary foods in infants. Research evidence best supports that which of the following food products is important to introduce into an infant's diet before age 1 year to prevent a specific allergy?

   A. Cow's milk
   B. Peanuts
   C. Sesame
   D. Soy
   E. Wheat

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2025 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2027, however, credit will be recorded in the year in which the learner completes the quiz.



2025 *Pediatrics in Review* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *Pediatrics in Review* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2025. To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.

5. During a 3-month-old infant's well-child visit, the mother raises concerns about her infant's risk for future food allergies. A neighbor's son is very limited in what he can eat because of "allergies," and she does not want a similar experience with her infant. As you provide anticipatory guidance regarding potential risk, what risk gradient ranking (highest to lowest) best reflects current consensus recommendations?

   A. Family history of atopy > other food allergies > severe eczema
   B. Family history of atopy > severe eczema > other food allergies
   C. Other food allergies > severe eczema > family history of atopy
   D. Severe eczema > family history of atopy > other food allergies
   E. Severe eczema > other food allergies > family history of atopy

A Review of Wilms Tumor

Valeria Smith, MD,[1] Andrew Wahba, MD,[1] Murali Chintagumpala, MD,[1] Priya Mahajan, MD[2]

[1]Texas Children's Cancer Center, Department of Pediatrics, Section of Hematology/Oncology, Baylor College of Medicine, Houston, Texas
[2]Seattle Children's Hospital, Department of Pediatrics, Division of Hematology, Oncology, Bone Marrow Transplant, and Cellular Therapies, University of Washington, Seattle, Washington

EDUCATION GAP

Wilms tumor is the most common renal malignancy in children. The pediatrician is often the first to encounter a Wilms tumor because affected children commonly present with an abdominal mass on clinical examination. Thus, the pediatrician should have a strong understanding of this tumor including the differential diagnosis, management, overall prognosis, and treatment-related late effects.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the differential diagnosis of pediatric renal tumors.
2. List syndromes associated with Wilms tumor.
3. Describe diagnostic and treatment modalities for Wilms tumor.

INTRODUCTION

Renal tumors account for 5% to 7% of all pediatric malignancies. Wilms tumor is the most common renal tumor in children under 15 years of age, representing approximately 600 new cases diagnosed in the United States each year. Long-term survival for patients with Wilms tumor is collectively greater than 85%.[1] Although favorable-histology Wilms tumor has an overall survival (OS) rate of 90%, other renal malignancies including anaplastic Wilms tumor, clear-cell sarcoma of the kidney, malignant rhabdoid tumor, and renal cell carcinoma (RCC) portend a less favorable outcome (Table 1).[2–10]

EPIDEMIOLOGY

The annual incidence of renal tumors in the United States is 7 cases per 1 million in children younger than 15 years of age, with Wilms tumor as the most frequent pediatric renal malignancy.[11,12] In contrast, RCC is more frequent in adolescents and young adults over the of age 15 years. There are ethnic variations in the incidence of Wilms tumor such that there is a greater risk in the Black population in the United States and a lower risk in Asians.[13]

Approximately 10% of children with Wilms tumor have an associated syndrome or congenital anomaly.[14] Thus, it is important to recognize the association and potential risk for developing Wilms tumor in patients with particular conditions or anomalies, such as WAGR (Wilms tumor, aniridia, genitourinary anomalies, and intellectual disabilities), Denys-Drash, (progressive nephropathy and male

AUTHOR DISCLOSURE: Drs Smith, Wahba, Chintagumpala, and Mahajan have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

BWS	Beckwith-Wiedemann syndrome
COG	Children's Oncology Group
CT	computed tomography
DD4A	dactinomycin, vincristine and doxorubicin
EFS	event-free survival
EE4A	dactinomycin and vincristine
LOH	loss of heterozygosity
MRI	magnetic resonance imaging
OS	overall survival
RCC	renal cell carcinoma
SIOP	International Society of Pediatric Oncology
VAD	vincristine, doxorubicin, and dactinomycin

TABLE 1. Primary Renal Malignant Tumors in Childhood

Renal Tumor	Incidence, %	Presentation	Prognosis
Wilms tumor	85–87	• Most common primary malignant renal tumor in childhood • Median age of diagnosis is 2 to 5 y of age • 5% to 7% present with bilateral disease • Claw sign on CT imaging	85%
Clear-cell sarcoma of the kidney	2–5	• Rare after age 4 y • Tend to metastasize to bone • Higher risk for late recurrences	80%
Mesoblastic nephroma	2–3	• Presents in the first 3 mos of life and 90% are diagnosed during the first year • Can be diagnosed prenatally and maternal polyhydramnios is often reported • Cellular variant has been associated with a higher risk of local recurrences and metastases than classic mesoblastic nephroma	Favorable with immediate surgical resection
Malignant rhabdoid tumor of the kidney	1–2	• Typically diagnosed at an age less than 3 y • Commonly present with extensive extrarenal metastasis at diagnosis • Associated with alterations in the *SMARCB1* gene	Poor
RCC	1–2	• Higher incidence of von Hippel-Lindau disease • Tends to be smaller in size than Wilms tumor at presentation and calcified in 25%	70%
Renal medullary carcinoma	<1	• Typically seen in adolescents and young adult African American patients with sickle cell hemoglobinopathy	Poor
Primary renal lymphoma	<1	• Rare type of non-Hodgkin lymphoma, accounting for 0.7% of all extranodal lymphoma • Commonly present as bilateral diffuse renal enlargement	Poor

Abbreviations: CT, computed tomography; RCC, renal cell carcinoma.

pseudohermaphroditism), Beckwith-Wiedemann syndrome (BWS) (hemihypertrophy, omphalocele, and macrosomia), Fanconi anemia, and Perlman syndrome (overgrowth feature, polyhydramnios and neonatal macrosomia).[15–17] These patients often have somatic or germline mutations involving *WT1, TRIM28, CTNNB1, NYNRIN, PALB2, WTX, TP53*, or have hypermethylation of the 11p15 region.[18–20]

For syndromes that have been associated with an increased risk for Wilms tumor, such as BWS, hemihypertrophy, Perlman, WAGR and Denys-Drash, active screening for Wilms tumor is important for early detection and can impact patient outcomes. Recommendations for Wilms tumor screening include a renal ultrasonography every 3 months starting at birth (or at diagnosis of the syndrome) through 7 years of age.[21] When feasible, these patients should be monitored closely by cancer predisposition experts.

PATHOGENESIS

Wilms tumor is thought to be caused by abnormal kidney development and may arise from foci of persistent metanephric cells (nephrogenic rests).[22] Furthermore, Wilms tumor has been associated with mutations of various tumor suppressor, transcription, and susceptibility genes, including *WT1*, *WT2*, familial *WT*, *WTX*, *CTNNB1*, and *p53* genes.[23–26] Gain of chromosome 1q and combined loss of heterozygosity (LOH) of chromosomes 1p and 16q have been associated with worse outcomes in patients with Wilms tumor.[27–29] LOH refers to a genetic alteration in which there is loss of one of the 2 alleles or loss of a copy of a DNA segment.

CLINICAL ASPECTS

Clinical Presentation

Most patients with Wilms tumor present with a unilateral solitary tumor, whereas approximately 7% to 10% have multifocal or bilateral disease at diagnosis.[30] The median age at diagnosis is 43 months in female children and 37 months in male children with unilateral disease; however, bilateral disease has a younger median age at diagnosis of 31 months in female children and 24 months in male children.[13]

Children with Wilms tumor often present with a large palpable abdominal mass or swelling. Other symptoms include hematuria (20%), flank pain, hypertension (25%), fever, and constipation at presentation.[31] Rarely do patients present with severe abdominal pain secondary to subcapsular

hemorrhage (which can occur in the presence of tumor rupture) or renal vein thrombosis (intravascular extension of tumor).

Diagnostic Evaluation

Children suspected to have Wilms tumor should be referred to pediatric oncology for further evaluation and care. Definitive diagnosis is confirmed by pathology through upfront nephrectomy or in rare cases, a biopsy.

Abdominal ultrasonography is a helpful initial study to evaluate for Wilms tumor and other abdominal masses. In children with suspected renal masses, a Doppler ultrasonography may be beneficial to detect tumor involvement of the renal vein and inferior vena cava. Ten percent of the patients have a tumor thrombus at diagnosis and thus the renal vein and inferior vena cava should be evaluated once a renal mass is detected.[32] A contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with and without contrast of the abdomen and pelvis is helpful to better characterize the renal mass, evaluate the renal vasculature and retroperitoneal lymph nodes, and further assess the contralateral kidney (Figure 1).[33] A CT of the chest is also recommended to evaluate for lung metastases.

Baseline laboratory studies for patients with suspected Wilms tumor include a chemistry panel, including serum creatinine, a complete blood count, urinalysis, a liver function panel, and a coagulation profile. Up to 8% of patients with Wilms tumor present with an acquired von Willebrand disease,[34] and therefore it is beneficial to obtain a von Willebrand assay preoperatively in patients who have a history of bleeding. The mechanism for this association is complex and may be attributed to Wilms tumor facilitating the binding of von Willebrand factor and removing it from circulation.[35]

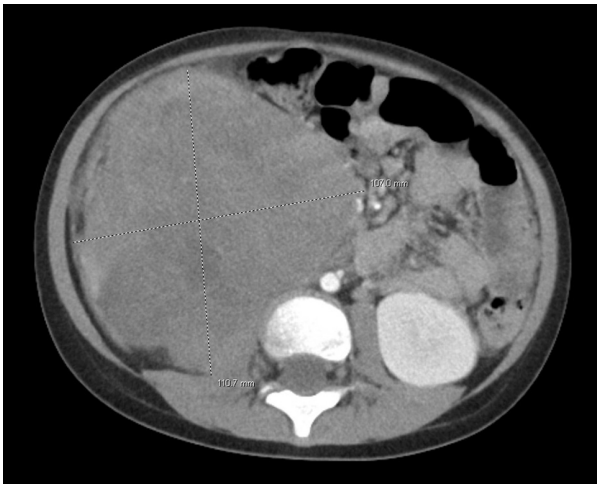


FIGURE 1. CT abdomen and pelvis with contrast demonstrating a large right heterogenous renal mass consistent with Wilms tumor. Abbreviations: CT, computed tomography.

Staging of Wilms tumor is based on age, extent of tumor involvement, tumor histology (favorable histology, focal anaplasia, or diffuse anaplasia Wilms tumor), and molecular and genetic markers.

MANAGEMENT

Most children with Wilms tumor receive multimodal therapy, which includes upfront nephrectomy when feasible, chemotherapy, and radiation therapy. Several prognostic factors, including patient age, stage, and tumor histology and biology, guide the management of Wilms tumor.

The Children's Oncology Group (COG) staging system for Wilms tumor is widely used in the United States and is based on surgical-pathologic data.[36] The COG approach includes upfront surgical intervention in all patients prior to any chemotherapy and/or radiation therapy. In contrast, the International Society of Pediatric Oncology (SIOP) approach to Wilms tumor, which is adopted by European pediatric oncology centers, uses upfront chemotherapy followed by surgical resection and additional chemotherapy and possible radiation. Both approaches yield comparable outcomes.

Surgical resection includes a nephrectomy and sampling of regional lymph nodes to assess for involvement. Surgical technique is important because the entire kidney needs to be removed without rupture of the renal cavity. Rupture of the renal cavity can lead to tumor spillage, which adversely impacts outcomes[37,38]; thus, these patients require more intensive chemotherapy.

Postoperative pathology further guides treatment for patients with Wilms tumor. The pathologist will determine if the tumor has favorable histology (no anaplasia) or has diffuse or focal anaplasia. This is important to distinguish for both treatment and prognosis because anaplasia is associated with a worse prognosis.[39,40] Additionally, the pathologist will determine the abdominal stage of the Wilms tumor. The COG staging for Wilms tumor classifies tumors as stage I through V based on the extent of disease, tumor spillage or rupture, lymph node involvement, and hematogenous spread (Table 2).[36] Tumors should be evaluated for LOH of 1p and 16q because this combination is associated with adverse outcomes[41,42] and requires more intensive chemotherapy.

Using pathology and the initial radiographic images, patients are risk-stratified to determine overall chemotherapy and radiation approaches. If a patient has a stage I favorable-histology Wilms tumor that weighs less than 550 g and is

TABLE 2. COG Staging for Wilms Tumor

Stage	Criteria
I	Tumor is limited to the kidney and completely resected
II	Tumor extends beyond kidney but completely resected (including thrombus in blood vessels)
III	• Residual tumor or nonhematogenous metastases confined to the abdomen • Positive lymph nodes • Positive surgical margins • Tumor spillage or biopsy
IV	Metastatic disease or spread beyond the abdomen (often lungs or distant lymph nodes)
V	Bilateral renal involvement

Abbreviation: COG, Children's Oncology Group.

under the age of 2 years, the patient is classified as very low-risk. In that case, no further treatment is needed, but the patient will be followed closely for recurrence.[43] Patients with disease localized to the kidney that was completely resected (stage I and II) receive 2-drug chemotherapy (dactinomycin and vincristine known as EE4A) for 19 weeks. Patients who have disease in the lymph nodes (stage III) or metastatic disease (stage IV) receive 3-drug chemotherapy (dactinomycin, vincristine, and doxorubicin known as DD4A) for 25 weeks. Cytogenetic testing of the tumor further risk stratifies Wilms tumor. As mentioned previously, patients who have positive LOH of both 1p and 16q will require chemotherapy that is more intensive. For example, those patients who were receiving EE4A would then receive DD4A, whereas those receiving DD4A would add cyclophosphamide and etoposide, known as Regimen M.

In addition to chemotherapy, some patients will require radiation therapy. Patients with stage III receive radiation, typically to the flank or hemiabdomen. Patients with metastatic lung disease will have a repeat chest CT at 6 weeks after the start of chemotherapy. If metastatic disease continues at week 6, the patient will receive whole lung radiation and chemotherapy will be intensified to Regimen M.[44,45]

Patients with anaplastic histology have a poorer outcome. Thus, they require more intensive chemotherapy compared with patients with favorable histology.[46] There are ongoing clinical trials to help determine the most effective regimen for these patients. The current COG clinical trial AREN1921 is a phase II trial for patients with newly diagnosed stages II through IV diffuse anaplastic Wilms and uses a UH-3 regimen, which consists of vincristine/doxorubicin/cyclophosphamide alternating with cyclophosphamide/carboplatin/etoposide, and vincristine/irinotecan for a total of 40 weeks. All patients with focal or diffuse anaplasia benefit from receiving radiation (flank/abdomen only for stages I-III).[39,47]

Stage V (bilateral Wilms tumor) is very complex and requires the care of a multidisciplinary team with experience in bilateral Wilms tumor. The goal for these patients is to craft a treatment plan that allows a cure while maintaining as much renal function as possible to prevent end-stage renal disease. The approach for these patients is to start with chemotherapy prior to surgery. The chemotherapy includes vincristine, doxorubicin, and dactinomycin in a regimen called VAD. Patients will receive 6 weeks of chemotherapy and then undergo imaging to determine if they are candidates for surgical resection. If nephron-sparing surgery is an option, the patient can undergo resection vs continuing VAD for 6 more weeks for a total of 12 weeks. At this time all patients should have their surgical resection. Given the complexity of bilateral Wilms tumor, discussions regarding surgery should involve a multidisciplinary team approach. Chemotherapy postsurgical resection is based on post-op pathology. This approach of chemotherapy followed by surgery has allowed better outcomes compared to historical controls with less incidence of end-stage renal disease.[48]

In contrast to COG, the European approach (SIOP) uses upfront chemotherapy based on the presence of metastatic involvement, followed by surgery. Patients with stages I through III (nonmetastatic) receive 4 weeks of neoadjuvant vincristine and dactinomycin. Patients with stage IV disease (metastatic) receive 6 weeks of vincristine, dactinomycin, and doxorubicin prior to surgery. Postoperatively patients are classified as low, intermediate, or high risk based on histology.[49] Low-risk includes pathology demonstrating 100% necrosis or no viable tumor. High-risk include patients with diffuse anaplasia or patients with greater than two-thirds of the viable tumor with blastemal histology. All others are considered intermediate risk. Postoperative chemotherapy is based on the histology and the stage. Postoperative chemotherapy varies from 4 weeks of EE4A (stage I, intermediate risk) to 34 weeks of doxorubicin, cyclophosphamide, carboplatin, and etoposide (stage IV, high risk). Radiation doses are increased for high-risk stages II through IV patients.

PROGNOSIS

In general, Wilms tumor has an overall excellent prognosis. Survival is dependent upon tumor histology, stage, and age of the patient at diagnosis. Patients with very low-risk Wilms tumors who only receive surgery have the best prognosis with a 4-year event-free survival (EFS) of 89.7% and OS of 100%.[43] Augmented therapy for stages I and II patients and stages III and IV with favorable-histology Wilms tumor with a combination of LOH of 1p and 16q have a 4-year EFS of 87.3% and 90.2%, respectively.[50] In comparison with

favorable unilateral histology Wilms tumor, patients with bilateral Wilms tumor have an inferior outcome. For patients with bilateral Wilms tumor, the 4-year EFS and OS are 82.1% and 94.9%, respectively.[48]

Patients with anaplastic Wilms tumor have the poorest prognosis, with the 4-year OS being 83%, 65%, and 33% for stages II, III, and IV, respectively.[39] Recurrent disease occurs in 15% of patients with favorable-histology Wilms tumor; however, this risk is increased to 50% in patients with anaplastic histology.[39] Recurrences often occur within the first 2 years of therapy and commonly involve the lungs.

Follow-up for patients with Wilms tumor who have completed therapy includes routine oncology care with surveillance for tumor recurrence and treatment-related effects. At the completion of therapy, patients are typically followed every 3 months for 2 years, then every 6 months for 2 years, and then annually for 1 year. Surveillance often includes abdominal and pulmonary surveillance.[51] This may include an abdominal ultrasonography and/or CT of the abdomen and pelvis in addition to a chest radiograph and/or CT of the chest. Patients will also undergo routine follow-up blood work to assess kidney function.

Survivors of Wilms tumor are at risk for late effects. Complications and late effects of management of Wilms tumor include renal impairment, cardiac toxicity, growth impairment, restrictive pulmonary disease, infertility, and secondary malignancies.[52–54] Thus, long-term follow-up for patients who received chemotherapy with/without radiation is essential. Individualized surveillance based on specific treatment exposures is critical for early identification and management of late therapy-related effects, and to improve quality of life. COG has developed risk-based clinical practice guidelines for surveillance and management of long-term treatment-related sequelae to guide the care of cancer survivors.[55,56] Although advances in understanding the implications of tumor biology and tailoring treatment approaches have improved the OS for children with Wilms tumor, further focus is needed to decrease late effects and improve outcomes for high-risk tumors, including anaplastic and bilateral Wilms tumor.

Summary

- Wilms tumor is the most common pediatric renal malignancy.[11,12] (Based on strong research evidence)
- There is an increased risk of developing Wilms tumor in children with certain syndromes, such as WAGR syndrome, Denys-Drash, BWS, Fanconi anemia, and Perlman syndrome.[15,16] (Based on strong research evidence)
- Tumor biomarkers including LOH 1p and 16q are incorporated into risk stratification, along with stage and histology for Wilms tumor to guide the overall management approach.[41,43] (Based on strong research evidence)
- Survivors of Wilms tumor are at risk for therapy-related late effects, which include renal failure, cardiac and pulmonary toxicity, infertility, and second malignant neoplasms.[52–54] (Based on strong research evidence)

Take the quiz! Scan this QR code to take the quiz, access the references, and view and save images and tables (available April 1, 2025).

PIR QUIZ

1. A previously well 4-year-old boy is brought to the pediatrician's office by his parents because of a swelling in the right side of the abdomen noted by the mother while she was bathing him the night prior. The child has been otherwise well, is up-to-date on all immunizations, and is active and playful. An abdominal ultrasonography is ordered, which shows the presence of a mass in the right kidney, with several enlarged lymph nodes near the renal hilum. In discussion with the mother of the need to see the pediatric oncologist, the pediatrician informs the mother that the most likely diagnosis for this child is which of the following?

   A. Clear-cell sarcoma of the kidney
   B. Malignant rhabdoid tumor of the kidney
   C. Mesoblastic nephroma
   D. RCC
   E. Wilms tumor

2. A 6-month-old boy is new to your practice. The child was born with an omphalocele and hemihypertrophy. The omphalocele was successfully repaired shortly after birth and a genetics clinic has given the child a diagnosis of BWS. Which of the following screening studies is the most appropriate to perform in this child?

   A. Abdominal ultrasonography every 3 months
   B. Analysis of blood cells for TP53 mutation
   C. Complete blood count twice per year
   D. Total body MRI yearly
   E. Whole-genome sequencing

3. A three-year-old girl who is followed in your clinic has recently been diagnosed with stage III Wilms tumor based on the finding of a renal mass and tumor resection showing favorable-histology Wilms tumor. The oncologist told the mother that there was a need for an additional analysis of the tumor tissue to help determine the intensity of chemotherapy needed. The mother calls you for help in understanding this. The oncologist is referring to additional testing that performs an analysis for which of the following?

   A. Chromosome 9:22 translocations
   B. HLA antigen typing
   C. LOH of chromosomes 1p and 16q
   D. P53 mutations
   E. WT 1 mutations

4. A five-year-old boy is found to have a left abdominal mass, which is felt to be consistent with Wilms tumor. On evaluation, the child is found to have on a CT study of the chest multiple nodules in both lungs. At the time of surgery, the pathology confirms Wilms tumor with favorable histology and the right kidney is free of disease. Which of the following best represents the stage of this child's disease?

   A. Stage I
   B. Stage II
   C. Stage III
   D. Stage IV
   E. Stage V

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2025 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*™, learners must demonstrate a minimum performance level of 60% or higher on this assessment. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2027, however, credit will be recorded in the year in which the learner completes the quiz.



2025 *Pediatrics in Review* is approved for a total of 30 Maintenance of Certification (MOC) Part 2 credits by the American Board of Pediatrics (ABP) through the AAP MOC Portfolio Program. *Pediatrics in Review* subscribers can claim up to 30 ABP MOC Part 2 points upon passing 30 quizzes (and claiming full credit for each quiz) per year. Subscribers can start claiming MOC credits as early as October 2025. To learn how to claim MOC points, go to: https://publications.aap.org/journals/pages/moc-credit.

5. A 3-year-old child is brought to your office with a left-sided abdominal mass. On evaluation, the child is found to have a large Wilms tumor in the left kidney and also has a focus of disease in the right kidney. The lungs are noted to be clear of disease by CT of the chest. The oncologist informs the parents that the child has stage V disease. Which of the following best represents the approximate 4-year EFS rate expected for this patient?

   A. 30%
   B. 50%
   C. 60%
   D. 80%
   E. 100%

INDEX OF SUSPICION

Torticollis and Hypoxia in a Febrile 3-Year-Old Girl

Roselyn Appenteng, MD, Lauren K. Kahl, MD

Division of Pediatric Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

PRESENTATION

A previously healthy immunized 3-year-old girl presents to the pediatric emergency department with neck pain. She has 11 days of fever, rhinorrhea, and cough with a maximum temperature of 104°F (40°C) on the day of presentation. She now has difficulty breathing while supine and difficulty moving her neck. Associated complaints include decreased oral intake and urine output and 1 episode of non-bloody diarrhea. Her mother denies any rashes, oral lesions, mucosal changes to the eyes, drooling, swelling of her extremities, choking or gagging episodes, or emesis. There is no recent travel or trauma. Vitals signs are as follows: temperature 102°F (38.9°C), heart rate 176 beats/min, respirations 40 breaths/min, blood pressure 119/66 mm Hg, and oxygen saturation 85% on room air. She is toxic appearing, with respiratory distress and left-sided torticollis with limited active and passive range of motion. Shotty anterior cervical lymph nodes are present bilaterally. She is able to open her mouth. She is tachypneic with diminished breath sounds throughout the left side and tachycardic without rubs, murmurs, or gallops. The abdominal exam is normal. Irritability is present, but the neurologic exam is otherwise normal. She has a negative Kernig sign. Capillary refill is less than 2 seconds, and there are no rashes, bruises, diaphoresis, or cyanosis. Her saturation improves (99%) on 1-L oxygen supplementation. The following tests are obtained as part of the institutional multisystem inflammatory syndrome in children protocol and for the prolonged fever: complete blood count, complete metabolic panel, inflammatory markers, troponin, pro-brain natriuretic peptide, blood culture, respiratory viral panel, and SARS-CoV-2 IgG antibody levels. A chest radiograph (Figure 1) and computed tomographic (CT) scan with intravenous contrast of the neck are obtained. She is positive for respiratory syncytial virus and negative for a current SARS CoV-2 infection on polymerase chain reaction testing. Her laboratory evaluation is notable for elevated neutrophils and bands despite a normal white count, microcytic anemia, mild thrombocytosis, and elevated inflammatory markers. Her blood culture is negative. In addition, she has a mildly elevated anion gap with a lactic acidosis, which corrects to normal range after a 20-ml/kg bolus of normal saline. Her laboratory evaluation is summarized in Table 1.

DISCUSSION

Differential Diagnosis

The differential diagnosis for acquired torticollis includes trauma, infection, central nervous system (CNS) and bone pathology, drug reaction, ocular pathology, and paroxysmal conditions. With a fever, specific diagnoses to consider include a

AUTHOR DISCLOSURE: Drs Appenteng and Kahl have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

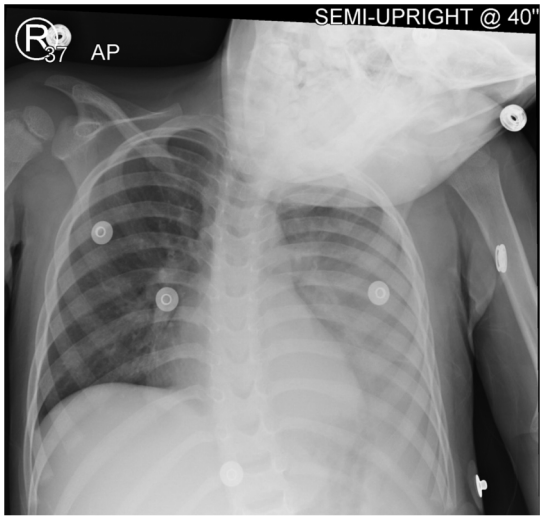


FIGURE 1. Anterior-posterior view of the patient's chest x-ray.

retropharyngeal abscess, acute cervical lymphadenitis, viral myositis, foreign body aspiration, Grisel syndrome (nontraumatic subluxation of the atlantoaxial joint), pneumonia with a parapneumonic effusion, cervical osteomyelitis, and cervical discitis.[1,2] Kawasaki disease presenting as a retropharyngeal abscess was also considered, in addition to COVID-19 and multisystem inflammatory syndrome in children. Other considerations for neck stiffness included meningitis and peritonsillar abscess.

Actual Diagnosis

Her chest x-ray (Figure 1) demonstrated diffuse opacification of the left lung. She had a normal para- and retropharyngeal space without atlantoaxial subluxation on the CT scan. A chest ultrasound on admission showed a medium-sized left pleural effusion and trace right pleural effusion. She was diagnosed with a superimposed bacterial pneumonia complicated by a parapneumonic effusion after a respiratory syncytial virus infection. Her torticollis was hypothesized to be secondary to referred pain.[1]

The Condition

Torticollis is a lateral head tilt associated with the chin rotated toward the contralateral side. It is a clinical sign and not a diagnosis. Congenital torticollis is the most common form.[1] Infection and trauma are the most common causes of acquired torticollis.[3,4] Children are vulnerable to cervical spine injuries with high-velocity traumatic injuries. Atlantoaxial subluxation is of particular concern during pediatric traumatic injuries when torticollis is a presenting sign.[4] Grisel syndrome, however, is a nontraumatic atlantoaxial subluxation. It is associated with head and neck infections as well as ear, nose, and throat surgeries and was considered high on the differential during this case prior to obtaining the CT scan.[5–7]

Upper respiratory tract infections, retropharyngeal and parapharyngeal abscess, cervical adenitis, and sternocleidomastoid myositis have been associated with torticollis.[4,6] Osteomyelitis, discitis, and pyomyositis should be considered if there is any concern for muscular or bony tenderness on exam. Rarely, Kawasaki disease and juvenile idiopathic arthritis have also been noted as the underlying diagnosis.[8–11] Although rare, pneumonia has been described as a cause of torticollis with referred pain from pleural irritation, with upper lobe pneumonia more commonly cited as underlying pathophysiology.[12] Additional life-threatening causes of pediatric torticollis include spinal and epidural hematomas, posterior fossa and spinal cord tumors, and suppurative jugular thrombophlebitis. CNS signs such as hypertension and bradycardia concerning for raised intracranial pressure, optic disk edema (indicating increased intracranial pressure), cranial nerve deficits, change in gait, extremity muscle weakness, or changes in bowel and bladder function may help to delineate CNS pathology from other causes of

TABLE 1. Laboratory Evaluation

Laboratory	Value	Reference Range
White blood cell count	11 510/μL (11.5 x 10^9/L)	6000–17 000/μL [6–17.0 x 10^9/L]
Neutrophils	69% (0.69)	14%–41% [0.14–0.41]
Hemoglobin	10.9 g/dL (109 g/L)	11.6–12.6 g/dL [116–126 g/dL]
Mean corpuscular volume	70.7 μm^3 (70.7fL)	75–87 μm^3 [75–87 fL]
Platelet count	360 000/μL (360 x 10^9/L)	150 000–350 000 /μL [150–350 x 10^9/L]
C-reactive protein	38.1 mg/dL	< 0.5 mg/dL
Erythrocyte sedimentation rate	123 mm/h	4–25 mm/h
Ferritin	499 ng/mL	13–150 ng/mL
Sodium	134 mEq/L (134 mmol/L)	135–148 mEq/L [135–148 mmol/L]
Chloride	94 mEq/L (94 mmol/L)	99–111 mEq/L [99–111 mmol/L]
Anion gap	20 mEq/L (20 mmol/L)	7–16 mEq/L [7–16 mmol/L]
Bicarbonate level	20 mEq/L (20 mmol/L)	21–31 mEq/L [21–31 mmol/L]

torticollis.[1,4] Neck tilt can also be a compensatory mechanism for diplopia, which may reflect ocular or CNS pathology.

It is important to ascertain if there is airway compromise in a patient exhibiting torticollis. Retropharyngeal abscess, parapharyngeal abscess, or brain stem mass can present with signs of upper airway obstruction or loss of airway maintenance. Pediatric patients may present with respiratory distress and hypoxia, as in this case, which may suggest an upper or lower respiratory tract infection. However, diaphragmatic paralysis because of CNS lesions must also be considered in context of the exam. Certain risk factors may increase predisposition to a particular cause. For example, children with Trisomy 21 have an increased risk of atlantoaxial instability, or a spinal or epidural hematoma may be more likely in the context of a hematologic disorder.

Management

Acquired torticollis is typically a transient clinical sign when the underlying pathology is appropriately treated. Diagnosing atlantoaxial subluxation is key to mitigating spinal trauma. Imaging typically includes x-rays with open-mouth odontoid, anterior-posterior, and lateral views. Since an odontoid view may be difficult to obtain in a pediatric patient with torticollis, a CT scan with contrast can be helpful in this evaluation, while also assessing for superficial and deep neck space infections or masses. If a CT scan demonstrates atlantoaxial subluxation, a magnetic resonance image is a better tool for diagnosing nonosseous spinal cord injury.[13] Neurosurgery involvement is key in determining if immediate intraoperative surgical intervention including cervical traction is needed vs conservative management with benzodiazepines for muscle relaxation and watchful waiting. Head imaging is warranted in the presence of CNS symptoms to rule out intracranial pathology. Otherwise, symptomatic management can include cervical collar placement and nonsteroidal anti-inflammatory drugs to help with inflammation and pain.[14,15]

Patient Course

The patient initially received empirical broad-spectrum antibiotics with ceftriaxone and vancomycin at meningitic dosing. Ibuprofen was given for antipyresis and pain management. A thoracostomy tube was used to drain the parapneumonic effusion after admission. She was quickly weaned off supplemental oxygen. Her antibiotic regimen was narrowed to ceftriaxone and sulfamethoxazole/trimethoprim and subsequently amoxicillin/clavulanic acid and sulfamethoxazole/trimethoprim for a total of 4 weeks. The patient's torticollis was the first sign to improve after admission.

LESSONS FOR THE CLINICIAN

- Pneumonia complicated by a parapneumonic effusion can present as acquired torticollis. Prolonged respiratory symptoms, hypoxia, and a febrile illness increase the likelihood of this diagnosis.
- It is important to determine if the torticollis is secondary to atlantoaxial subluxation on imaging since neurosurgical management would be indicated.
- Acquired torticollis secondary to infectious causes such as a parapneumonic effusion resolves with adequate pain management and with resolution of the primary illness.

References for this article can be found at
https://doi.org/10.1542/pir.2023-006088

INDEX OF SUSPICION

Jaundice Developing in a 13-Day-Old Baby With Down Syndrome

Shane Clark, MD,[1] Annette Roberts, MD, MPH,[2] Paul Suhocki, MD,[3] Samrat Das, MD[1]

[1]Duke University School of Medicine, Department of Pediatrics, Durham, North Carolina
[2]Duke University School of Medicine, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Durham, North Carolina
[3]Duke University School of Medicine, Department of Interventional Radiology, Durham, North Carolina

PRESENTATION

A 13-day old term female infant with trisomy 21 who previously had normal transcutaneous bilirubin screenings in the first few days of life develops jaundice overnight. She was born via planned Cesarean delivery to a 40-year-old female individual at 39 weeks' gestation and required a hospitalization following birth for respiratory distress. Initially, during her neonatal intensive care unit stay, she was treated with intermittent low-flow nasal cannula support with 0.1 to 0.3 L of oxygen per hour. She was found to have a moderately sized atrial septal defect (ASD) and a large patent ductus arteriosus (PDA) that was diagnosed shortly after birth. She was started on furosemide (1 mg/kg) daily for suspected pulmonary edema.

For the last 3 days, the patient has had poor oral feeding intake. Today, she weighs 5% less than her birth weight. Previously, she was tolerating full oral feeds at a rate of 150 mL/kg/d of human breast milk and is now only consuming around 100 mL/kg/d. Her physical examination this morning shows an alert and active infant with conjunctival icterus and jaundice of the face and body. Her facial features are distinct, with upward slanting of the palpebral fissures that appear consistent with trisomy 21. The lungs are clear to auscultation, with no audible murmurs, and the abdomen is nontender, nondistended, and soft to palpation. A soft liver tip is palpated at the right costal margin, and no splenomegaly is appreciated. Total serum bilirubin level obtained this morning is elevated to 15.6 mg/dL with a conjugated bilirubin of 8.5 mg/dL and an unconjugated bilirubin of 7.1 mg/dL. Additional laboratory tests show an elevated aspartate aminotransferase (AST) of 446 U/L, alanine aminotransferase (ALT) of 436 U/L, and alkaline phosphatase of 607 U/L. The international normalized ratio (INR) is normal at 1.0. Thyroid studies show a normal thyroid stimulating hormone of 1.82 μIU/mL and a free thyroxine 4 (T_4) of 1.92 ng/dL. Complete blood count shows a normal white blood cell count of 11×10^9/L and hemoglobin level of 18.4 g/dL. Ammonia level is normal at 49 μmol/L.

AUTHOR DISCLOSURE: Drs Clark, Roberts, Suhocki, and Das have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

DISCUSSION

Differential Diagnosis

Jaundice is a commonly occurring condition in neonates, with unconjugated hyperbilirubinemia being the predominant etiology.[1] Unconjugated hyperbilirubinemia

is typically less pathological in nature, including causes such as benign neonatal jaundice, ABO incompatibility, hemolytic anemia, breast milk jaundice, and breast feeding jaundice.[2] Although its etiology can be benign, unconjugated jaundice still needs to be closely monitored, as high levels can lead to Kernicterus. The American Academy of Pediatrics (AAP) recommends routine checking of bilirubin in every infant within 24 hours before discharge.[3] Additionally, they advise measuring total and direct bilirubin levels in breastfed infants presenting with jaundice at age 3 to 4 weeks and in formula-fed infants at age 2 weeks.[3] On the other hand, conjugated hyperbilirubinemia is defined as a conjugated bilirubin level greater than or equal to 2.0 mg/dL or greater than 20% of the total bilirubin level.[4] It is always considered pathological and requires a thorough workup.[5] Conjugated hyperbilirubinemia developing shortly after birth is referred to as neonatal cholestasis. Neonatal cholestasis affects around 1 infant out of every 2500 births.[6] Cholestasis is often a result of hepatic injury and can be caused by the obstruction of bile flow, issues with transportation of bile, or systemic disease, which can affect bile formation.[4] Biliary atresia, a form of extrahepatic biliary obstruction, is the most common cause of neonatal cholestasis present in approximately 25% to 35% of all cases of neonatal cholestasis.[4,5] Other identifiable causes include congenital and acquired infections, parenteral nutrition-associated liver disease, endocrinopathies, drug- or toxin-induced hepatic injury, metabolic diseases (ie, alpha-1 antitrypsin, cystic fibrosis, galactosemia, tyrosinemia), choledochal cysts, heart failure, and genetic disorders such as Alagille syndrome and progressive familial intrahepatic cholestasis.[4]

Initial workup for infants presenting with conjugated hyperbilirubinemia should include a thorough laboratory workup. Markers of liver synthetic function, including prothrombin time, ammonia, and albumin, are important to acquire because abnormal values indicate advanced hepatic injury and may warrant more rapid evaluation and intervention.[4] AST and ALT are typically elevated to a variable degree but are not specific for a cause of cholestasis.[4] Urinalysis and urine culture should also be part of the initial workup to rule out a urinary tract infection, as well as blood cultures if clinically indicated because infections can result in elevated conjugated bilirubin levels. It is also important to review the infant's newborn screen to rule out inborn errors of metabolism.[4] Liver Doppler ultrasonography should also be obtained as part of the initial workup to evaluate the liver, gallbladder, and bile ducts and assess for any vascular abnormalities that may be contributing to the clinical picture.[7] In the case of our patient, initial laboratory tests showed a conjugated bilirubin level of 8.5 mg/dL and evidence of hepatic injury as depicted by the elevated liver enzymes. Liver synthetic function appeared normal given the appropriate INR level. Our team obtained a liver Doppler ultrasonography, which showed a dilated left portal vein with increased velocity involving its connection with the hepatic vein. This study was followed-up with an abdominal computed tomography (CT) scan, which identified multiple portosystemic shunts involving the left portal and left hepatic veins with an enlarged suprahepatic inferior vena cava and hepatic artery as a result of the shunting.

The Condition

The patient was diagnosed with a rare condition called a congenital portosystemic shunt (CPSS). CPSS is thought to occur in 1 out of 50 000 births and can be associated with genetic syndromes, most commonly trisomy 21.[8,9] CPSS is caused by an abnormal connection between portal and systemic veins that forms due to a failure of involution of specific primordial vessels.[10] This results in complete or partial diversion of portal blood flow away from the liver to the systemic venous system. CPSS can lead to cholestasis and complications such as end-stage liver disease liver tumors, portopulmonary hypertension, and pulmonary arteriovenous shunts.[11] Imaging is critical for diagnosis, as it is uncommon, and clinical findings are often nonspecific.[11] Liver ultrasonography with Doppler, which often shows enlargement of the portal or systemic venous system, is the preferred first-line imaging modality, as well as a useful tool for follow-up after treatment.[12] CT or magnetic resonance imaging is then used to confirm the diagnosis, better characterize the vascular malformations, and guide future interventions if they are indicated.[11] In most cases, intrahepatic shunts will close spontaneously within the first year of life. For this reason, interventions should only be considered in patients who are older than age 1 year or in patients with associated complications such as poor fetal hemodynamics, growth restriction, respiratory distress, and hepatic inflammation.[13] Given our patient's oxygen requirement and poor feeding, a decision was made to undergo procedural treatment in our patient's case. Percutaneous closure often performed by an interventional radiologist is preferred over surgical management.[11] During percutaneous closure, the vessel is treated by intravascular embolization, most often using plugs or coils. Most patients improve following shunt closure, with heart and liver complications typically resolving completely within months following the procedure.[11]

Following further discussion between our team and our hepatology colleagues, the patient was taken for percutaneous shunt embolization by our interventional radiology team.

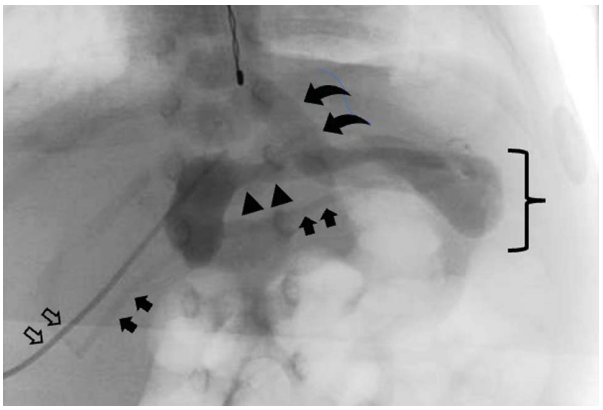


FIGURE 1. Portal venography with iodinated contrast demonstrates tip of transhepatic catheter (open arrows) in an enlarged left portal vein. A large branch of the left portal vein (arrowheads) communicates directly with the left hepatic vein (curved arrow) via a large congenital portal-systemic shunt (bracket). Two smaller portal-systemic shunts (arrows) are also present.

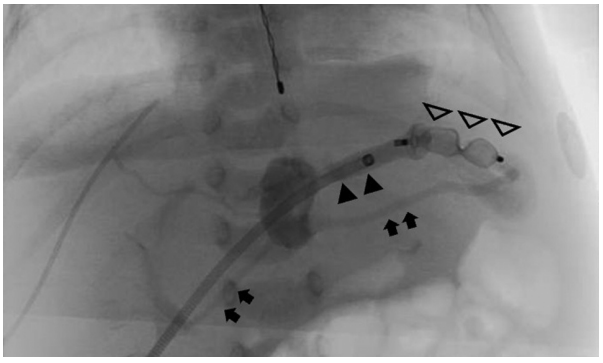


FIGURE 2. Postembolization portal venography demonstrates the tip of a vascular sheath (arrowheads) in the left portal vein branch that previously communicated with the left hepatic vein. The portal vein branch is now occluded by an embolic device plug (open arrowheads), and the hepatic vein no longer fills with contrast. Two smaller portal-systemic shunts (arrows) remain patent.

Transhepatic portal venography demonstrated 2 small portosystemic shunts and a dominant shunt between the left portal vein and the hepatic vein (Figure 1). The dominant shunt was occluded with a 7-mm diameter embolic device plug on day of life (DOL) 24 (Figures 2, 3). The 2 smaller shunts were left untreated. Two days after the procedure, the patient's bilirubin began to decrease (total bilirubin, 12.8 mg/dL; direct bilirubin, 7.8 mg/dL), and the patient was weaned to room air.

Our patient was discharged home on DOL 33 with pulmonology, hepatology, cardiology, and special infant care

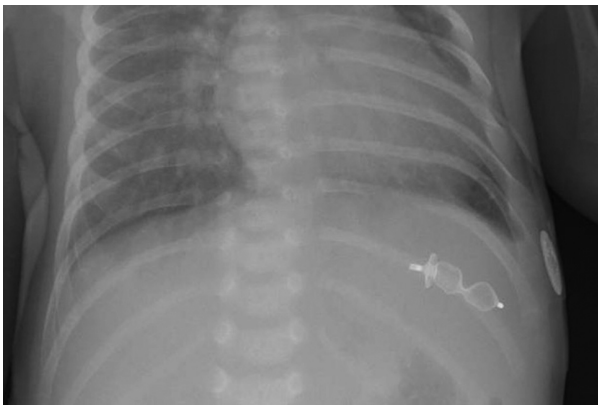


FIGURE 3. Postembolization anterior-posterior chest radiograph demonstrates an embolic device plug in the expected location of the left hepatic lobe.

clinical follow-up. Since discharge, the patient has been clinically stable and is doing well. She is gaining weight and developing appropriately. She remains asymptomatic and without jaundice. Most recent laboratory tests including INR, liver enzymes, ammonia level, conjugated and unconjugated bilirubin levels have all been within normal limits. Repeat liver ultrasonography showed interval closing of the small shunts that were not embolized and sustained closure of the main portosystemic shunt. Repeat follow-up echocardiogram showed a small PDA, moderate ASD, and no pulmonary hypertension, which were improved from admission and expected to resolve with time.

Lessons for the Clinician

- Jaundice in early life should be evaluated by obtaining a fractionated serum bilirubin level to examine total, conjugated, and unconjugated bilirubin levels.
- Conjugated hyperbilirubinemia, defined as a conjugated bilirubin level greater than or equal to 2.0 mg/dL or greater than 20% of the total bilirubin level, is concerning and always requires further diagnostic testing and evaluation.
- CPSS should be considered in the differential diagnosis for conjugated hyperbilirubinemia.
- Liver Doppler ultrasonography is the preferred initial imaging modality used to identify CPSS.
- Small CPSSs can resolve on their own. However, symptomatic patients require intervention by a team of interventional radiologists.

References for this article can be found at
https://doi.org/10.1542/pir.2023-006234

INDEX OF SUSPICION

Chest Pain and Weight Loss in a 10-Year-Old Girl

Helen Zhou, MD,[1] Alvin P. Chan, MD, MPH,[1] Alireza Sedarat, MD,[2] Esther Jun-Ihn, MD[1]

[1]Division of Pediatric Hospitalist Medicine, Department of Pediatrics, UCLA Mattel Children's Hospital, Los Angeles, California
[2]Division of Pediatric Gastroenterology, Department of Pediatrics, UCLA Medical Center, Los Angeles, California

PRESENTATION

A 10-year-old girl with history of food allergies and eczema presents to the emergency department for acute chest pain and "vomiting." She was eating earlier when she suddenly developed a severe squeezing and burning pain at the center of her chest. She expelled the food immediately, but the pain persisted, prompting her mother to bring her to the hospital. For the past 8 months, she has been having a similar type of localized and nonreproducible chest pain during meals, but it has always spontaneously resolved within 30 minutes. Along with the pain, she has been throwing up chunks of undigested food daily without gagging, retching, and nausea, during and immediately after meals. Initially, she had difficulty swallowing solids only, but now she struggles with both solids and liquids despite being hungry. She feels like food is stuck in her throat. She has no bloody or bilious emesis. She endorses normal stool patterns with no blood. In total, she has lost 40 pounds since symptom onset.

After multiple visits with her pediatrician and local emergency department, she was found to have normal basic laboratory and imaging results including normal complete blood count, basic metabolic panel, amylase, lipase, chest x-ray (CXR), and magnetic resonance imaging noncontrast brain scan. She was subsequently diagnosed as having bulimia nervosa and gastroesophageal reflux disease. She was started on famotidine and takes no other medications. She was provided mental health resources, including a therapist, with no improvement in symptoms.

Despite the diagnosis of bulimia nervosa, the patient, mother, and stepfather, together and separately, deny any history of distorted body image, social media triggers, or family history of eating disorders or mood disorders. They also deny any eating disorder behaviors, such as fear of weight gain, laxative use, binge eating, excessive exercise, food rituals, or diet pills. The patient does not report any bullying or major life stressors.

On review of systems, she endorses generalized, nonlocalized, dull headaches that are not associated with her chest pain or eating. She has no history of recent illnesses, fevers, travel, chills, difficulty breathing, cough, ingestions, rashes, or joint pain. She has a history of anaphylaxis to fish but denies any exposures.

On examination, she has a temperature of 37 °C, heart rate of 82 bpm, respiratory rate of 20 breaths/minute, blood pressure of 86/53 mm Hg, and oxygen saturation of 98% on room air. She has a body mass index of 11.8 kg/m^2 (z score = −1.16). Her affect is flat and general appearance is thin. Her respiratory examination shows clear breath sounds bilaterally with no stridor or wheezing. Her abdomen is soft, nondistended, and non-tender. Her hands are free from any scrapes or calluses.

AUTHOR DISCLOSURE: Drs Zhou, Chan, Sedarat, and Jun-Ihn have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

TABLE 1. Initial Laboratory Evaluation on Admission

Component	Value	Reference Range and Units
Sodium	142 (142)	135–146 mEq/L (135–146 mmol/L)
Potassium	2.6 (2.6)[a]	3.6–5.3 mEq/L (3.6–5.3 mmol/L)
Chloride	116 (116)[a]	96–106 mEq/L (96–106 mmol/L)
Total carbon dioxide	16 (16)[a]	20–30 mEq/L (20–30 mmol/L)
Urea nitrogen	27 (9.6)[a]	7–18 mg/dL (2.5–6.4 mmol/L)
Creatinine	0.62 (54.8)	0.6–1.3 mg/dL (53–114.9 μmol/L)
Phosphorus	3.7 (1.2)[a]	4–5.6 mg/dL (1.3–1.8 mmol/L)
Lipase	30 (0.5)	13–69 U/L (0.2–1.15 μkat/L)
Troponins	<0.4	0.0–51.4 ng/L

Data in parentheses are Système International (SI) units.
[a]These values are outside of reference range.

She has no lanugo or dermatitis. She also has no dental caries or parotid enlargement. She is alert and appropriately interactive with a normal neurologic examination. The rest of her physical examination is unremarkable. During the interview, the patient is voraciously eating a sandwich, pausing intermittently to regurgitate chunks of food into the basin without apparent distress. She is not retching or heaving.

Laboratory evaluation, shown in Table 1, is consistent with hypokalemic, hyperchloremic metabolic acidosis, likely from dehydration and insufficient intake. The 12-lead electrocardiogram shows normal sinus rhythm with a heart rate of 95 bpm. An ultrasound scan of her abdomen with doppler and CXR shows no abnormalities. Gastroenterology is consulted, and the patient is admitted to the hospital for further workup and nutritional optimization. Parenteral nutrition was started to restore the nutritional deficits and prevent further wasting; electrolytes were monitored frequently for refeeding syndrome.

DISCUSSION

Differential Diagnosis

The most notable features of this case are regurgitation, dysphagia, and weight loss. Regurgitation is the passive ejection of material from the esophagus, not usually associated with discomfort or nausea. This contrasts with vomiting, which is the forceful expulsion of contents from the stomach. The patient's presentation is more in line with regurgitation than vomiting, narrowing the differential diagnosis to either an esophageal motility disorder or a structural obstruction, such as eosinophilic esophagitis (atopic history), food impaction, achalasia, rumination syndrome, peptic stricture, or extrinsic esophageal compression from intrathoracic tumor or vascular ring. Most of these disorders can also cause dysphagia, but motility disorders are more likely to result in dysphagia to both solids and liquids.

With such profound weight loss, other causes were considered on the differential diagnosis, including celiac disease, inflammatory bowel disease, gastroparesis, hyperthyroidism, and eating disorder, specifically bulimia nervosa. These conditions were ruled out on admission given the normal celiac panel, fecal calprotectin, and thyroid-stimulation hormone results. Although lower on the list, increased intracranial pressure was also considered, but this was ruled out given normal recent brain imaging. After discussion with our adolescent eating disorder specialists and additional input from our gastrointestinal specialists, our medical team concluded that she did not meet the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for an eating disorder, specifically bulimia nervosa. The Pediatric Columbia Suicide Rating Scale on admission was negative. Our patient was not vomiting out of compulsion but rather regurgitating, and this was repeatedly assessed after monitoring her eating in the hospital.

Actual Diagnosis

Early in the admission, a barium swallow study showed a dilated thoracic esophagus that tapered at the gastroesophageal junction with no extrinsic mass effect and no passage of contrast through the esophagus (bird's beak sign) (Figures 1 and 2). The next day, an upper gastrointestinal endoscopy



FIGURE 1. Barium swallow study with a classic "bird's beak" sign of a 10-year-old with dysphagia and malnutrition.



FIGURE 2. Barium swallow study with a classic "bird's beak" sign.

with biopsy and esophageal manometry was performed to exclude esophagitis and malignancy that can mimic achalasia. Endoscopy revealed a narrowed distal esophagus with no strictures, food impaction, or anatomic variation (Figures 3 and 4). Manometry demonstrated high pressure in the lower esophageal sphincter (LES) at rest and a failure to relax after swallowing, confirming the diagnosis. Esophageal biopsy samples found no eosinophilia or other

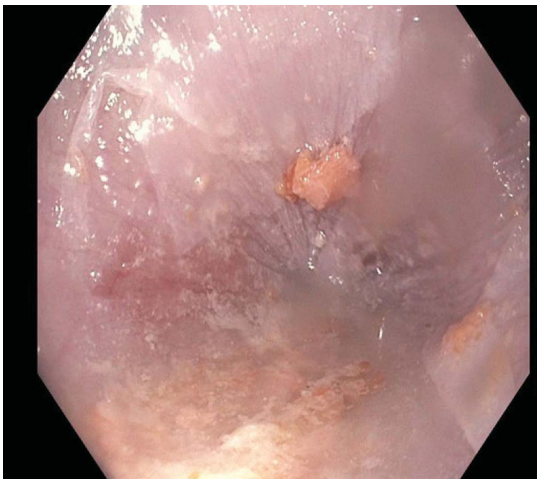


FIGURE 3. Endoscopy photos before peroral endoscopic myotomy with retained contents.

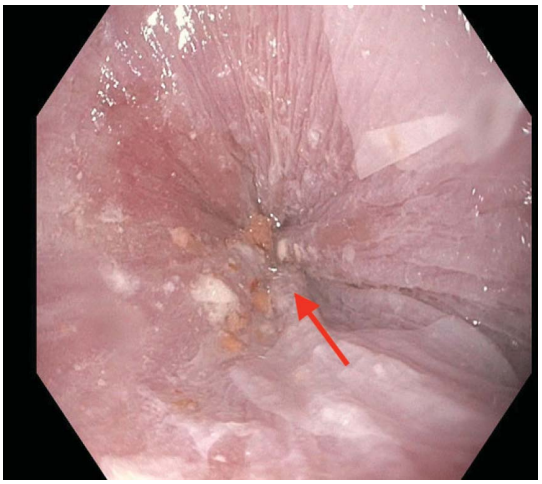


FIGURE 4. Endoscopy photos before peroral endoscopic myotomy with pooled secretions owing to tight lower esophageal sphincter.

inflammation on histology, ruling out eosinophilic esophagitis or other infections such as cytomegalovirus or candidal esophagitis.

The Condition

Achalasia is a neurodegenerative disorder characterized by degeneration of the myenteric plexus that results in dysfunction of LES smooth muscle and loss of organized peristalsis.[1] Achalasia in children is often misdiagnosed, particularly for gastroesophageal reflux disease, leading to a 6- to 10-year delay in treatment.[1] The estimated global incidence rate ranges from 0.03 to 1.63 per 100 000 children per year.[2] The etiology is unknown, but symptoms are related to nerve damage in the esophagus. The most common presenting signs are regurgitation, dysphagia, weight loss, food bolus obstruction, chest pain, nocturnal cough, and chronic aspiration. The chest pain seen in achalasia is more common in younger individuals.[3] Although the exact cause of the pain is unclear, it seems to be an age-dependent phenomenon related to visceral hypersensitivity.[3]

The initial evaluation includes barium swallow, upper gastrointestinal endoscopy, and esophageal manometry (gold standard). Once diagnosed, the severity of disease can be quantified using the Eckardt scale (Table 2). Our patient had an Eckardt score of 10 (range, 0–12).[3]

Treatment/Management

Achalasia is treated either pharmacologically or mechanically to decrease the pressure in the LES. Endoscopic pneumatic balloon dilation weakens the LES by tearing its smooth muscle fibers.[1] Injection of botulinum toxin into the LES inhibits the neurons that increase smooth

TABLE 2. Eckardt Scale: the Final Score Is the Sum of the 4 Symptom Scores, Ranging From 0 to 12

	Score			
Symptom	**0**	**1**	**2**	**3**
Dysphagia	None	Occasional	Daily	With every meal
Regurgitation	None	Occasional	Daily	With every meal
Chest pain	None	Occasional	Daily	With every meal
Weight loss, kg	0	<5	5–10	>10

muscle tone to decrease the muscle tone in the LES.[1] Although effective, both methods are temporary and require repeated treatments. Nitrates and calcium channel blockers are the least effective options and must be given before meals to relax the LES. Surgical myotomy, generally considered the standard and definitive treatment for achalasia, is often performed in conjunction with a surgical antireflux procedure to reinforce the cut LES muscle fibers.[1]

Peroral endoscopic myotomy (POEM) is the newest therapy to treat achalasia, originally done only in adults but now also increasingly in children.[1,4] POEM involves an endoscopic incision to the esophageal mucosa, creation of a submucosal tunnel, and a cut through the muscularis propria of the LES.[1,4] Compared with surgical myotomy, POEM is equally effective but less invasive with shorter recovery.[1,4] The most common long-term complication is esophageal reflux, which can be evaluated by repeat upper endoscopy, and serious adverse effects are few.

Patient Course

After the diagnosis was confirmed, the patient underwent a POEM (Figures 5–7). She had a barium swallow study done the following day, which did not show any leakage or perforation. She started on liquids for the first meal, then advanced to a soft diet. She was discharged home after 1 day with a soft diet and eventual transition to a regular diet at 2 weeks. She did not need any feeding rehabilitation after evaluation from occupational therapists, and no vitamin supplementation was needed after discharge given normal vitamin D and iron levels during the hospitalization. She was also maintained on a proton pump inhibitor to prevent post-POEM esophageal reflux. At her 4-week follow-up, she had complete resolution of her presenting symptoms with improving weight gain and energy (Eckardt score 0). She was scheduled for a routine surveillance upper endoscopy with pH monitor at 6 months after POEM to assess the efficacy of the procedure and the



FIGURE 5. Upper endoscopy photos of the mucostomy during peroral endoscopic myotomy.

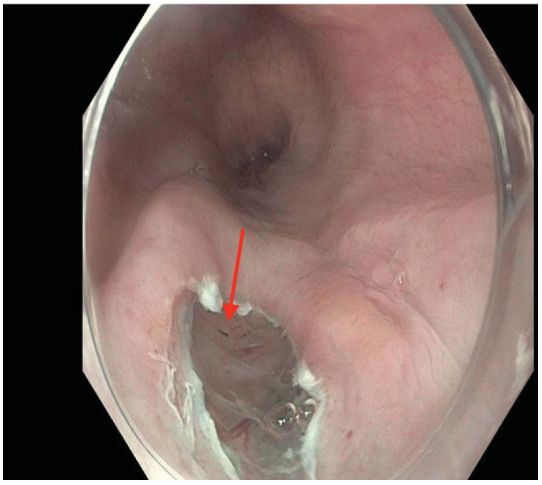


FIGURE 6. Upper endoscopy photos of the tunnel with myotomy during peroral endoscopic myotomy.

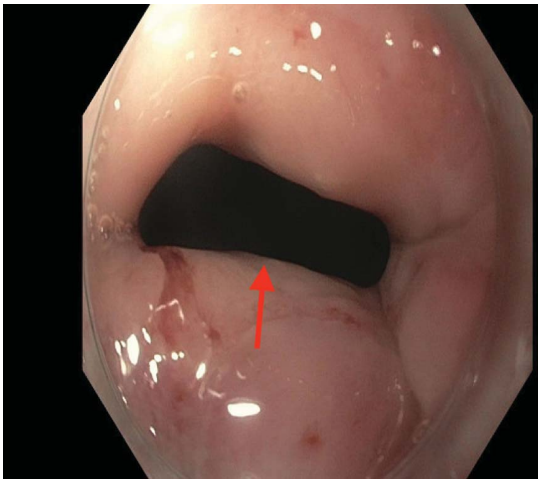


FIGURE 7. Upper endoscopy photos of the open and relaxed lower esophageal sphincter after peroral endoscopic myotomy.

presence of acid reflux. This found adequately treated achalasia with no signs of acid reflux, and her body mass index improved to 15.6 kg/m^2 (z score = –0.83) from a 21-pound weight gain.

LESSONS FOR THE CLINICIANS

- Achalasia is a rare cause of regurgitation and dysphagia that can also present with chest pain, electrolyte abnormalities, and severe malnutrition.
- Despite some differences in symptoms, achalasia can be mistaken for an eating disorder, particularly in adolescent girls. A careful medical history is key to making an accurate diagnosis.
- Regurgitation is differentiated from vomiting by the effortless expulsion of undigested content from the esophagus shortly after eating, not typically associated with retching or nausea.

References for this article can be found at
https://doi.org/10.1542/pir.2023-006130

INDEX OF SUSPICION

Purulent Right Ankle Wound in a 3-Year-Old Boy

Jose A. Elizondo-Leal, MD,[1] Brenna Parker, MD,[1] Rebecca C. Brady, MD,[2,3] Melissa D. Klein, MD, MEd[3,4]

[1]Housestaff Office, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[2]Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[3]University of Cincinnati College of Medicine, Cincinnati, Ohio
[4]Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

PRESENTATION

A 3-year-old, fully immunized, nonverbal boy with autism spectrum disorder presented to the emergency department in March with a 2-day history of a right ankle pustule and pain. The pustule had worsened despite daily washing with soap and water and topical neomycin/polymyxin B/bacitracin ointment. He remained afebrile but developed an antalgic gait and refused to bear full weight; he was still able to toe walk. Examination revealed a right lateral ankle pustule with a central punctum and surrounding 1-cm area of erythema, swelling, and tenderness. No tests or imaging were performed. Oral cephalexin and topical mupirocin were prescribed for suspected cellulitis, and he was discharged home.

Despite medication adherence, the boy's right ankle swelling, erythema, and pain worsened. He developed spontaneous drainage of purulent fluid from the wound, fever of 102 °F (38.9 °C), and refusal to bear weight, prompting a return to the emergency department 3 days later.

The boy's parents denied recent travel, preceding injury, history of skin disorders, boils or staphylococcal infection, or exposure to animals or bodies of water. He lives in Cincinnati. He had been closely observed when playing outside at parks. He had not been camping nor playing in the woods. His parents did not recall any insect bites or exposure to ticks, fleas, or arachnids.

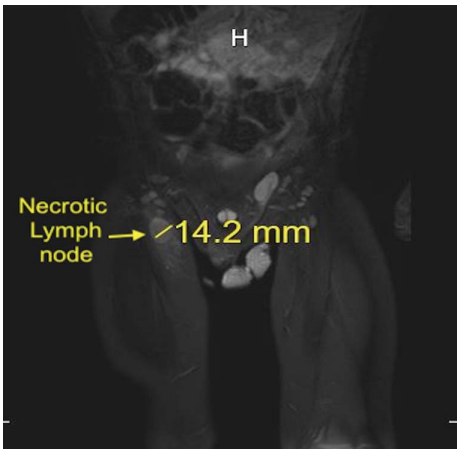
Physical examination revealed a well-appearing boy in pain with vital signs as follows: temperature 100.0 °F (37.8 °C), heart rate 152 beats/min, respiratory rate 28 breaths/min, blood pressure 97/61 mm Hg. There was a 3 × 1 cm area of erythema and induration with central skin breakdown and scant purulent drainage on the right lateral ankle just superior to the lateral malleolus (Figure 1). He refused to bear weight and resisted dorsiflexion of the right foot. He grimaced with palpation of the right gastrocnemius muscle. Movement of the right knee, right hip, and left leg was normal, and there was no inguinal lymphadenopathy. Bilateral dorsalis pedis and posterior tibial pulses were 2+, and capillary refill was 2 seconds.

Laboratory studies were significant for a white blood cell (WBC) count of 17 300/μL (17.3×10^9/L) (reference range 6000–17 000/μL [$6.0–17.0 \times 10^9$/L]) with an absolute neutrophil count of 12 060/ μL (12.06×10^9/L) (reference range 1500–8500/μL [$1.5–8.5 \times 10^9$/L]). C-reactive protein (CRP) was 5.31 mg/dL (53.1 mg/L) (reference range ≤0.3 mg/dL [≤3 mg/L]), and erythrocyte sedimentation rate was 12 mm/h (reference range 0–10 mm/h). Gram stain of the purulent

AUTHOR DISCLOSURE: Drs Elizondo-Leal, Parker, Brady, and Klein have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.



FIGURE 1. Skin of right lateral ankle, which demonstrates erythema and central punctum.



FIGURES 2. Coronal view of magnetic resonance imaging with contrast of the right inguinal lymph nodes demonstrating necrotic right inguinal lymphadenopathy.

drainage demonstrated many WBCs but no organisms. Aerobic wound and blood cultures were sent. Right ankle radiograph showed soft-tissue swelling without fracture or osseous erosion. Due to treatment failure on cephalexin and inability to walk, the boy was admitted to the hospital.

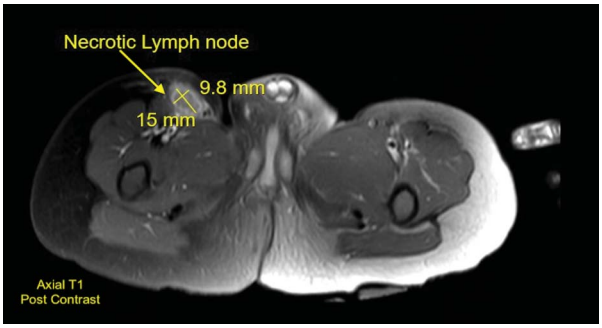
DISCUSSION

Differential Diagnosis

Initial differential diagnosis focused on cellulitis, osteomyelitis, septic arthritis, and/or necrotizing fasciitis. Upon admission, intravenous (IV) clindamycin (40 mg/kg/d) was initiated to cover for methicillin-resistant *Staphylococcus aureus* and anaerobes. His pain was controlled with scheduled acetaminophen and ibuprofen. With the unremarkable exposure history, nontuberculous mycobacterial and fungal infections seemed less likely. His medical history was not suggestive of immunodeficiency. Given his inability to bear weight, there was concern for progression to osteomyelitis or septic arthritis. Necrotizing fasciitis was considered; however, the lack of rapidly progressing erythema and absence of soft-tissue crepitus and vesicular or bullous lesions reassured against this diagnosis.

Actual Diagnosis

On hospital day (HD) 1, a sedated magnetic resonance imaging was ordered to better characterize the lesion and help determine an adequate empirical treatment. It revealed extensive soft-tissue cellulitis with myofasciitis (Figures 2 and 3) extending from the distal right thigh to the ankle joint and significant right inguinal and popliteal lymphadenopathy with necrotic components (Figures 4 and 5). There was no evidence of osteomyelitis or septic arthritis. Given the degree of involvement and concern for progression to necrotizing soft-tissue infection, plastic surgery was consulted,



FIGURES 3. Cross sectional view of magnetic resonance imaging with contrast of the right inguinal lymph nodes demonstrating necrotic right inguinal lymphadenopathy.

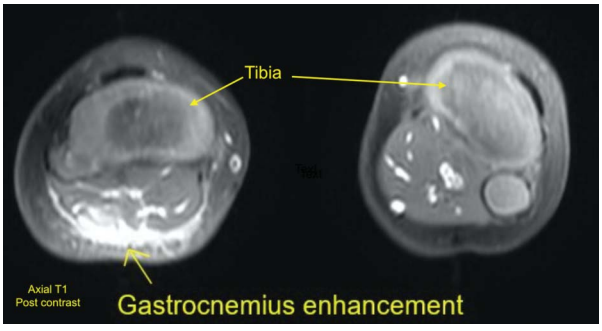


FIGURE 4. Magnetic resonance imaging with contrast of the right leg demonstrating gastrocnemius myofasciitis.

which recommended chlorhexidine gluconate soaks and warm compresses to the right ankle, as tolerated, with close monitoring.

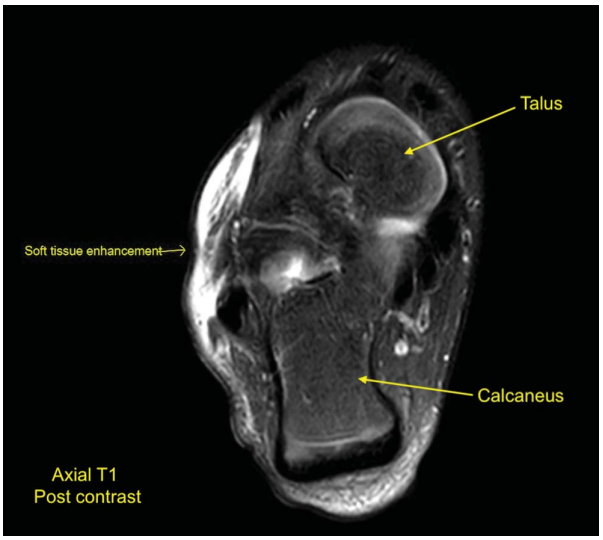


FIGURE 5. Magnetic resonance imaging with contrast demonstrating cellulitis with myofasciitis extending to right ankle

On HD 2, the blood and wound cultures remained negative. Repeat CRP was 5.6 mg/dL (56 mg/L). The child remained afebrile and hemodynamically stable on IV clindamycin; however, his right ankle wound had minimal improvement. Gram stain of the purulent drainage again demonstrated WBCs but no organisms. A repeat aerobic wound culture was sent. The infectious disease service was consulted and recommended adding rifampin (20 mg/kg/d) for improved tissue penetration.

By HD 3, the erythema and drainage had decreased. Repeat CRP was 3.6 mg/dL (36 mg/L). Aerobic wound cultures on blood and chocolate agar plates grew dry, cream-colored, pitted colonies, and Gram stain revealed beaded Gram-positive branching rods. The organism was acid fast on modified Ziehl-Neelsen stain, suggesting *Nocardia*. The boy was diagnosed with primary lymphocutaneous nocardiosis, likely acquired through an unrecognized penetrating injury with environmental contamination given the presence of a central punctum on first presentation.

The Condition

Nocardia are Gram-stain–positive, aerobic, filamentous bacilli that are ubiquitous saprophytes found in water, soil, and decaying organic matter.[1] Immunocompetent individuals typically acquire *Nocardia* through traumatic inoculation of the skin and soft tissues, which results in cutaneous or ascending lymphocutaneous disease. *Nocardia* often acts as an opportunistic pathogen in immunocompromised hosts. It is often acquired through inhalation of dust particles resulting in pulmonary nocardiosis and can have hematogenous dissemination to the bone, brain, or skin.[2–4] Those with T-cell–mediated immune dysfunction (eg, transplant patients receiving immunosuppressive medications, patients with HIV infection, patients on chronic high-dose corticosteroid therapy or calcineurin inhibitors) and neutrophil defects (eg, chronic granulomatous disease [CGD]) are at greatest risk of pulmonary or disseminated disease.[1–3,5] Skin and soft-tissue infections can also be seen in immunocompromised individuals.[2]

Isolation of *Nocardia* species from appropriate clinical specimens (eg, wound drainage with cutaneous disease or respiratory specimens with pulmonary disease) confirms the diagnosis.[1] *Nocardia* stains Gram-stain positive and weakly or partially "acid fast" by modified Kinyoun or Ziehl-Neelsen staining with light microscopy.[6] Species identification and susceptibility reports usually require testing in a reference laboratory.[7]

Treatment/Management

Trimethoprim/sulfamethoxazole (TMP/SMX) is the antibiotic of choice for empirical treatment of localized or mild *Nocardia* infections.[1] However, certain *Nocardia* species, including *Nocardia farcinica* and *Nocardia nova*, may have intrinsic resistance to TMP/SMX.[8,9] Therefore, combination antibiotic therapy is recommended for empirical treatment of immunocompromised patients and those with serious disease (eg, pulmonary, central nervous system, or disseminated disease) until identification and susceptibilities return.[1] Identification of the specific *Nocardia* species can aid in choosing the second antibiotic to overcome resistance.

Primary cutaneous and lymphocutaneous infections are most often associated with *Nocardia brasiliensis*.[4] Immunocompetent individuals usually improve after 6 to 12 weeks of TMP/SMX monotherapy.[1]

Immunocompromised patients with pulmonary disease should have cerebrospinal fluid and/or neuroimaging studies because *Nocardia* has a propensity for hematogenous spread to the brain.[1] If brain abscesses are present, antibiotics that cross the blood–brain barrier (eg, TMP/SMX, carbapenems) are recommended.[2] Immunocompromised patients and those with serious infections are treated for at least 6 to 12 months and for at least 3 months after apparent cure due to the propensity for relapse.[1]

Patient Course

The second wound culture also grew *Nocardia* after approximately 72 hours of incubation. The blood culture remained sterile. Clindamycin and rifampin were stopped on HD 3. The severity of infection, association of *Nocardia* infections with CGD, and the boy's young age raised concern for possible immunodeficiency. As such, the infectious disease

team recommended initiation of dual therapy with oral TMP/SMX (15 mg/kg/d) and IV ceftriaxone (50 mg/kg/d) until further identification and susceptibilities returned. On HD 5, the wound culture identified *N brasiliensis*, which was unexpected given that this species is most often associated with tropical and subtropical environments,[10] and he had not traveled to these areas. Given most strains of *N brasiliensis* are susceptible to amoxicillin/clavulanate,[4,8,9] coupled with its excellent bioavailability, the infectious disease team recommended transitioning from IV ceftriaxone to oral amoxicillin (90 mg/kg/d)/clavulanate to continue dual therapy with TMP/SMX until immunologic testing (flow cytometric neutrophil oxidative burst and pneumococcal titers) and susceptibilities returned. He was discharged home on HD 6 to continue dual therapy.

Flow cytometric neutrophil oxidative burst was normal, and he had appropriate pneumococcal antibody titers in response to his prior pneumococcal conjugate (13-valent) vaccine series. Based on these results, the boy was deemed immunocompetent. Susceptibility testing at the University of Texas Health Center at Tyler, Department of Microbiology Research, Mycobacteria/Nocardia Laboratory confirmed the isolate as *N brasiliensis* susceptible to TMP/SMX, amoxicillin/clavulanate, linezolid, tobramycin, and moxifloxacin 8 days after discharge.[11] Amoxicillin/clavulanate was stopped. CRP level after 18 days of appropriate antibiotics was normal. The boy completed 3 months of TMP/SMX, and the wound healed without complication.

LESSONS FOR THE CLINICIAN

- Consider *Nocardia* infection in patients with persistent symptoms of pneumonia, cavitary lung lesions on imaging, and/or skin findings that may be associated with soil-contaminated trauma, such as pustules, penetrating injury, abscesses, cellulitis, and lymphangitis.
- Individuals with T-cell impairments (eg, bone marrow and solid organ transplant recipients on immunosuppressive medications, patients with HIV, those with history of cytomegalovirus, those on high-dose corticosteroid therapy or calcineurin inhibitors) or CGD are at highest risk of infection and disseminated disease.
- Due to the neurotropic nature of *Nocardia* and propensity for hematogenous spread, patients with suspected or confirmed *Nocardia* infection require thorough evaluation for disseminated disease and consideration of immunodeficiency.
- TMP/SMX is the antibiotic of choice for empirical treatment of localized or mild *Nocardia* infections. In the case of immunocompromised individuals or serious disease, combination antibiotic therapy is recommended until susceptibilities result.

References for this article can be found at
https://doi.org/10.1542/pir.2023-006259

IN BRIEF

Prevention Strategies for RSV Infection in Infants

Shannon Glenn-Otto, MD, Adam Dziacky, MD

Department of Pediatric and Adolescent Medicine, Johns Hopkins All Children's Hospital, Saint Petersburg, Florida

Respiratory syncytial virus (RSV) causes acute upper and lower respiratory tract infections in people of all ages. RSV is usually associated with upper respiratory symptoms; however, infants and children are more likely to develop lower respiratory disease during primary infection. Symptoms in children usually begin with rhinorrhea and decreased appetite, followed by cough, fever, and wheezing, and symptoms may progress to include respiratory distress and lethargy.

RSV is the most common reason for hospitalization in infants and is responsible for a large burden of severe illness in children. Although children with prematurity, lung disease, and congenital heart disease are at increased risk of severe illness, most cases of RSV occur among previously healthy children. Approximately 30% of infants will acquire RSV, and 2% to 3% of these infants will require hospitalization. Studies estimate that RSV is associated with 15% of all office visits for respiratory tract infections from November to April, and 2.1 million children aged under 2 years seek outpatient care for RSV infections annually. Inpatient treatment may include oxygen supplementation, rehydration, and/or mechanical ventilation, the cost of which totals $709.60 million annually in the United States.

Despite the high incidence and cost, current treatment options for RSV are limited and based on supportive care measures. Researchers have been attempting to develop a successful and safe infant RSV vaccine since the 1960s. Initially, a formalin inactivated RSV vaccine was developed. During a randomized control trial, the incidence of medically attended RSV infections and severe symptoms was higher in the group receiving the vaccine than the control, and 2 children in the vaccine group died upon natural exposure to RSV. Children who received the vaccine did not develop neutralizing antibody titers comparable with those who had undergone natural infection. It was concluded the formalin inactivation had altered protein epitopes, which resulted in near complete loss of neutralization sensitive antibody epitopes and potentiated disease through the formation of immune complexes in the lung. As a result, there remain lingering safety concerns regarding the administration of nonreplicating vaccines. Live-attenuated vaccines have offered potential in infants; however, developing a vaccine that balances achieving sufficient attenuation while retaining immunogenicity remains a significant challenge. Virus vectored vaccines have shown promise in phase 1 safety and immunogenicity trials; however, they remain many years away from trials in seronegative infants. Recent developments in alternative prevention strategies offer hope in reducing the burden of RSV.

Beyfortus (nirsevimab-alip; manufactured by AstraZeneca AB; distributed by Sanofi Pasteur, Inc) is a human recombinant monoclonal antibody that binds to the prefusion conformation of the RSV F protein. The attachment of nirsevimab to the F protein prevents the virus from entering the cells that line the respiratory

AUTHOR DISCLOSURE: Drs Glenn-Otto and Dziacky have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. Griffin MP, Yuan Y, Takas T, et al; Nirsevimab Study Group. *N Engl J Med.* 2020;383(5):415–425.

Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices–United States, 2023. Jones JM, Fleming-Dutra KE, Prill MM, et al. *MMWR Morb Mortal Wkly Rep.* 2023;72(34):920–925.

Palivizumab Prophylaxis in Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. Caserta MT, O'Leary ST, Munoz FM, Ralston SL; Committee on Infectious Diseases. *Pediatrics.* 2023;152(1):e2023061803.

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. Kampmann B, Madhi SA, Munjal I, et al; MATISSE Study Group. *N Engl J Med.* 2023;388(16):1451–1464.

Use of the Pfizer Respiratory Syncytial Virus Vaccine During Pregnancy for the Prevention of Respiratory Syncytial Virus-Associated Lower Respiratory Tract Disease in Infants: Recommendations of the Advisory Committee on Immunization Practices–United States, 2023. Fleming-Dutra KE, Jones JM, Roper LE, et al. *MMWR Morb Mortal Wkly Rep.* 2023;72:1115–1122.

tract, allowing viral neutralization. In a randomized clinical trial, only 1.2% of infants who received nirsevimab contracted medically attended RSV-associated lower respiratory tract infection (LRTI) compared with 5.0% in the placebo group. Medically attended RSV LRTI was defined by 3 criteria: (1) RSV confirmed by polymerase-chain-reaction assay, (2) signs of lower respiratory tract disease, and (3) signs of severe respiratory disease. Overall, nirsevimab was 74.5% effective in preventing medically attended infection.

The US Food and Drug Administration (FDA) approved nirsevimab in 2023 for the prevention of RSV in infants and children aged up to 24 months. Shortly following approval, the American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP) recommended nirsevimab for infants and children meeting criteria. Nirsevimab is recommended for all infants aged less than 8 months starting their first week of life if the following criteria are met: (1) it is just before or during RSV season (October through March, although this time frame may vary geographically); and (2) the mother did not receive a RSV vaccine during pregnancy, the mother's RSV vaccination status is unknown, or the infant was born less than 14 days after maternal vaccination. Children with increased risk conditions should also receive a dose during their second RSV season. Increased risk conditions defined by the ACIP are listed in Table 1.

The dosage of 50 mg administered intramuscularly (IM) is recommended for infants who weigh less than 5 kg, and 100 mg IM is recommended for infants exceeding this weight limit. Two 100 mg injections administered simultaneously are recommended for children aged between 8 and 19 months who meet criteria for administration during their second season. Possible adverse effects include injection site reactions and rash. Contraindications include severe allergic reactions to nirsevimab or any of its components.

In general, previous infection, even during the same RSV season, should not be considered a factor in determining nirsevimab eligibility because RSV infection does not confer long-lasting immunity. Children who received palivizumab in their first season are eligible for nirsevimab in their second season if they meet the increased risk criteria. Palivizumab should not be administered if a child receives nirsevimab during RSV season because a single dose of nirsevimab offers protection for at least 5 months. Children can receive 1 dose of nirsevimab if they have received less than 5 doses of palivizumab during the RSV season.

According to the AAP, private-sector cost for nirsevimab is approximately $520 per dose. Due to unprecedented demand for nirsevimab after its approval, there was a shortage during the first RSV season it was available (Winter 2023–2024). Nirsevimab developers are working on increasing the supply for the Winter 2024 to 2025 season.

In contrast to nirsevimab, which is offered for all infants, Synagis (palivizumab; manufactured by Swedish Orphan Biovitrum AB) is cost effective for specific populations of children. Palivizumab is a humanized mouse recombinant monoclonal antibody, which was approved for use in 1998. It also binds the F protein, giving it neutralizing and fusion inhibitory activity; however, it has a significantly shorter half-life compared with nirsevimab. In a randomized clinical trial, it was found that children 35 weeks gestational age or less and children with bronchopulmonary dysplasia who received 5 monthly injections of palivizumab had a 55% relative reduction in hospitalization due to RSV compared with the placebo group.

Palivizumab is recommended for the following populations when aged less than 12 months at the beginning of RSV season: (1) infants born at or before 28 weeks and 6 days gestation, (2) infants with chronic lung disease, and (3) infants with hemodynamically significant congenital heart disease. It is also recommended for children aged up to 2 years who have chronic lung disease of prematurity that requires therapy. Limitations include the need for monthly administration and the cost. The average cost of palivizumab treatment during the 2016 to 2017 season ranged from $3221 to $12 568 (this wide range is due to differences in birth months, which determine the number of doses administered per season).

Alternative strategies for preventing RSV in infants include maternal vaccination during pregnancy. Abrysvo (RSV vaccine; manufactured by Pfizer Inc) is approved for

TABLE 1. Increased Risk Conditions for Medically Attended RSV Infection

Children with chronic lung disease of prematurity who required medical support (ongoing corticosteroid therapy, diuretic therapy, or supplemental O_2) any time during the 6-mo period before the start of the second RSV season	
Children with severe immunocompromise	
Children with cystic fibrosis who have either	Manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first y of life or abnormal findings on chest imaging when stable)
	Or wt-for-length <10th percentile
American Indian or Alaska Native children	

Abbreviation: RSV, respiratory syncytial virus.

administration to pregnant females between 32 0/7 and 36 6/7 weeks of gestation to prevent RSV LRTI in infants. Although months may vary geographically, administration should occur between September and January. Abrysvo contains RSV prefusion F glycoprotein from subgroups A and B, thus inducing an immune response in the recipient after injection. Randomized clinical trial results showed 81.8% vaccine efficacy within 90 days after birth and 69.4% vaccine efficacy within 180 days after birth in preventing medically attended severe RSV-associated lower respiratory tract illness in infants born to mothers vaccinated with Abrysvo vs mothers that received the placebo. Infant protection is expected to wane due to decreasing concentration of transplacentally acquired maternal antibody over time. Currently, there are no data regarding the efficacy of the first lifetime dose to protect infants born after subsequent pregnancies. Possible side effects for neonates include low birth weight (5.1% Abrysvo vs 4.4% placebo) and jaundice (7.2% Abrysvo vs 6.7% placebo). The price range is estimated between $305 and $320 per dose. Abrysvo and 2 additional vaccines (Arexvy manufactured by GlaxoSmithKline Biologicals and mResvia manufactured by Moderna) have also been approved for the prevention of severe RSV in patients aged 60 years or older.

RSV in infants and children is associated with a substantial health and economic burden. Treatment remains supportive. The introduction of antibody products for infants and vaccination for expectant mothers offer promising data in protection from RSV. Although palivizumab was approved in 1998 for high-risk infants for the prevention of RSV, it has significant limitations related to cost, the need for monthly administration, and current qualifying conditions. Both nirsevimab for infants and the RSV vaccine for expectant mothers promise more widespread protection. These developments could remarkably alter the current burden of RSV disease morbidity and mortality. Logistics, including cost, distribution, and parental acceptance and uptake, remain barriers to widespread use.

Comments: This In Brief reminds me of the marvels of scientific discovery and continued research to address critical health care issues. I still remember the licensure of palivizumab by the FDA in June of 1998. While it is so important to have a strategy for RSV prevention for those infants at highest risk, the process of identifying those eligible infants at high risk, the high cost of doses of medication, and challenges for infants to receive monthly doses over a 5-month period required vigilant medical staff and quality improvement initiatives to have effective ways to make this prevention feasible. A major limitation was that it was only available to infants who met high-risk eligibility requirements, and epidemiologic data have shown that RSV infection can affect infants without high-risk conditions. Great progress has been made in the development of a human recombinant monoclonal antibody, which is available to all infants and can be administered 1 time per RSV season with special considerations for an additional dose the subsequent season for those infants who are considered at high risk. While it is very exciting to have a vaccine for pregnant women and older populations, my hope is that a vaccine for infants and children will be available soon. Again, we are so fortunate as a population to benefit from the public health measures and vaccine development that save children's lives.

Janet Serwint, MD
Associate Editor, In Brief

Acknowledgment

We would like to thank Dr Matthew Thomas, Pediatric Infectious Disease Specialist, for his thoughtful review and editing of this article.

ANSWER KEY FOR APRIL PEDIATRICS IN REVIEW

Impact of Natural Disasters on Children: Key Considerations for Pediatricians:
1. A; 2. E; 3. A; 4. A; 5. D
Food Introduction in Infancy:
1. B; 2. B; 3. A; 4. B; 5. E
A Review of Wilms Tumor:
1. E; 2. A; 3. C; 4. D; 5. D

IN BRIEF

Inflammatory Markers in Pediatrics

Lingxiao Viviano, MD, Margaret Huntwork, MD

Tulane University School of Medicine, New Orleans, Louisiana

INTRODUCTION

Inflammatory markers are substances in the blood that increase in response to inflammation, typically rising during infection, injury, rheumatoid and autoimmune conditions, malignancy, and chronic diseases. Inflammatory markers commonly used in pediatric practice include erythrocyte sedimentation rate (ESR), ferritin, C-reactive protein (CRP), procalcitonin (PCT), and calprotectin. The utility of these markers varies depending on the clinical indication and the acuity of the illness. This review article provides an overview of common inflammatory markers, including their biological origins, utility in certain conditions, normal ranges, and implications for real-time clinical decision-making.

ESR

ESR measures how quickly red blood cells (RBCs) settle in a vertical sedimentation tube over 1 hour, expressed in millimeters per hour. Normally, RBCs repel each other due to the negative charge from sialic acid on their membranes. During inflammation, the liver produces fibrinogen, which is positively charged and reduces the negative charge on RBC membranes, causing them to adhere. This aggregation decreases resistance in the plasma, increasing the ESR. A higher ESR indicates faster RBC settling and inflammation. ESR typically rises within 1 to 2 days of inflammation onset but takes weeks to return to baseline due to fibrinogen's half-life of about 7 days. Clinically, elevated ESR levels are seen in diverse conditions ranging from sickle cell vaso-occlusive crises to infection to systemic and localized inflammatory conditions.

Kawasaki disease (KD) is a systemic vasculitis that usually affects children aged 5 years and younger and is a common cause of acquired heart disease in children. KD can cause moderate to severe elevations in ESR due to widespread systemic inflammation. Patients with KD treated with intravenous immunoglobulin therapy (IVIG) may have worsening ESR elevations after IVIG due to the aggregator effect of globulin on RBCs.

FERRITIN

Ferritin, an iron storage and transport protein, is a commonly used inflammatory marker. In the setting of bacterial infection, elevated ferritin levels play a pivotal role in sequestering iron, thereby impeding a pathogen's access to the body's iron stores. Ferritin levels typically rise within 1 to 2 days after the onset of inflammation or infection, peak within 5 to 7 days, and take weeks to normalize after an inflammatory response.

AUTHOR DISCLOSURE: Drs Viviano and Huntwork have disclosed no financial relationships relevant to this article. This commentary does not contain discussion of unapproved/investigative use of a commercial product/device.

Use of C-Reactive Protein and Ferritin Biomarkers in Daily Pediatric Practice. Taylor MD, Allada V, Moritz ML, et al. *Pediatr Rev.* 2020;41(4):172–183.

Utility of Procalcitonin as a Biomarker for Sepsis in Children. Downes KJ, Fitzgerald JC, Weiss SL. *J Clin Microbiol.* 2020;58(7):e01851–19.

The Use of Fecal Calprotectin Testing in Paediatric Disorders: A Position Paper of the European Society for Paediatric Gastroenterology and Nutrition Gastroenterology Committee. Koninckx CR, Donat E, Benninga MA, et al. *J Pediatr Gastroenterol Nutr.* 2021;72(4):617–640.

Biomarkers for Kawasaki Disease: Clinical Utility and the Challenges Ahead. Chaudhary H, Nameirakpam J, Kumrah R, et al. *Front Pediatr.* 2019;7:242.

Hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) are overlapping, life-threatening conditions characterized by excessive immune activation and inflammation leading to severe tissue damage. Hyperferritinemia is observed in HLH/MAS, along with a low ESR level (due to hypofibrinogenemia) and an elevated CRP level. Monitoring ferritin levels is crucial for diagnosing and managing HLH/MAS. Specialized biomarkers like soluble interleukin 2 receptor α, interleukin 18, and chemokine ligand 9 may be more specific for HLH/MAS; however, their results are not immediately available for early decision-making.

Hyperferritinemia can also be seen in the settings of transfusion dependence, viral or bacterial infection, stem cell transplant, malignancy, and renal disease. In children who are critically ill, ferritin levels that exceed 1000 ng/mL, especially when accompanied by high CRP levels, indicate immune system hyperactivation and are associated with higher odds of pediatric intensive care unit admission and mortality.

CRP

CRP is another commonly used inflammatory marker, predominantly synthesized by the liver in response to interleukin 6. CRP binds phosphocholine on the surface of bacteria and necrotic cells, enhancing opsonization and activating the classical complement cascade.

CRP and ESR are often ordered in tandem under certain clinical circumstances, with their results interpreted in combination to provide a better understanding of the clinical situation. Compared with ESR, CRP exhibits a more rapid rise and fall, often rising within hours and peaking within 48 hours. This rapid response makes CRP particularly useful in detecting early acute infections or inflammation. Whereas ESR may take weeks to normalize due to the long half-life of fibrinogen, CRP levels typically return to normal shortly after effective therapy is initiated. This distinction between ESR and CRP can help differentiate between an acute insult and a chronic process.

Infections are likely to cause both CRP and ESR elevations. The degree of CRP elevation may relate to the extent of infection. For instance, myositis is likely to cause higher CRP elevations compared with a superficial skin infection.

CRP also has great utility in monitoring response to treatment for infectious conditions. In pediatric osteomyelitis, both ESR and CRP are typically elevated at admission. Whereas ESR generally peaks 2 days after effective treatment begins and declines slowly over weeks, CRP decreases more rapidly, within 2 to 3 days. Both CRP and ESR usually normalize by the end of the treatment course.

Unlike ESR levels, CRP levels are not influenced by elevated plasma protein concentrations that may occur: for example, during treatment with IVIG.

Of note, CRP is typically not elevated in patients with active systemic lupus erythematosus (SLE) disease (exceptions include cases of serositis and infection in a patient with active SLE disease). Active SLE disease is associated with elevated interferon alpha, which suppresses CRP.

PCT

PCT is the precursor protein to calcitonin, predominantly produced by the thyroid gland. In healthy individuals, it is undetectable. PCT levels increase in response to bacterial

TABLE 1. Comparison of Common Inflammatory Markers in Pediatrics

Marker	Clinical Utilities	Typical Time of Response	Significant Elevation
ESR	Aids in diagnosis of inflammatory and infectious conditions; monitoring response to treatment; distinguishing acute vs chronic inflammation	Rises within 1–2 d, normalizes over weeks	>40 mm/hr[a]
Ferritin	Aids in the diagnosis of inflammatory and infectious conditions including HLH/MAS; stratifying malignant conditions; monitoring iron status	Rises within 1–2 d, peaks in 5–7 d, normalizes over weeks	≥500 ng/mL, with levels >1000 ng/mL concerning for HLH/MAS[a]
CRP	Aids in the diagnosis of inflammatory and infectious conditions; monitoring response to treatment; distinguishing acute vs chronic inflammation	Rises within 4–6 h, peaks in 2 d, normalizes within 7–10 d	≥1 mg/dL[a]
Procalcitonin	Aids in antibiotic use decision-making; levels may be elevated in invasive bacterial infections	Rises within 2–3 h, peaks in 1–2 d, normalizes in 2–3 d	>0.5 ng/mL may indicate bacterial infections
Fecal calprotectin	Aids in distinguishing inflammatory from non-inflammatory gastrointestinal conditions; negative test may be helpful to rule out inflammatory bowel disease	Rises within 1–2 d, stable over >1 week	>50 μg/g (feces)

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome.
[a]Normal ranges for these markers differ by age.

toxins and cytokines including lipopolysaccharides from bacterial membranes. PCT exhibits a swift rise and fall, typically peaking around 24 to 48 hours. False elevations may occur within the first 48 hours after birth due to various maternal and perinatal factors.

Because bacterial toxins and cytokines cause increased production of PCT, PCT levels are commonly used to differentiate between bacterial and nonbacterial processes in pediatric practice. Interferon gamma, commonly elevated during viral infections, inhibits PCT production. Thus, elevated PCT levels are typically associated with bacterial infections, particularly pneumonia, meningitis, and other invasive bacterial infections. Normal PCT results can occur in localized infections like tonsillitis, sinusitis, cellulitis, or abscess. In the right clinical setting, PCT has the potential to guide antibiotic use.

Elevated PCT levels can also be seen in patients receiving immunomodulatory agents, those with severe liver disease, inflammatory disorders (including KD), and neuroendocrine tumors. Mild elevations may also be observed in patients with malaria, invasive candida, and pulmonary mold infections. Notably, immunocompromised status does not affect PCT production.

CALPROTECTIN

Calprotectin is a complex of proteins that sequester metals such as calcium and zinc. It is located in the cytosol of neutrophils. During an inflammatory process of the gut, neutrophils migrate to the gastrointestinal tract, and calprotectin becomes detectable in the feces.

Fecal calprotectin typically increases with an increasing degree of inflammatory activity in the gastrointestinal tract. Levels rise quickly and remain stable over weeks. Fecal calprotectin is used as a biomarker to distinguish inflammatory from noninflammatory gastrointestinal conditions. Fecal calprotectin has a high sensitivity and moderate specificity for inflammatory bowel disease in children compared to blood inflammatory markers. It also has a high negative predictive value; normal tests may prevent unnecessary gastroenterologist referrals and costly endoscopies. Fecal calprotectin can also be elevated in infectious diarrhea, with higher concentrations often observed in acute bacterial diarrhea compared with viral diarrhea.

LIMITATIONS

The clinical utility of inflammatory markers is tempered by limitations. Inflammatory markers can be influenced by a variety of factors, potentially leading to false-negative or false-positive results. Studies investigating inflammatory markers demonstrate variability in definitions, normal ranges, and methodology, making it difficult to directly compare these tests across different diseases and settings. Understanding limitations is crucial to prevent overreliance.

CONCLUSION

Inflammatory markers are helpful tools in the diagnosis and management of inflammation, infections, injuries, autoimmune conditions, malignancies, and chronic diseases. Table 1 compares helpful features of inflammatory markers discussed in this article. Clinicians must be mindful of the implications of ordering these tests, with a clear understanding of pitfalls, timing, and potential causes of abnormal results. Interpretation of elevated inflammatory marker levels should always be made in conjunction with the patient's overall clinical picture.

Comments: Most of us will have reason to order inflammatory marker tests in the course of evaluating febrile infants. In the past, we relied on an elevated white blood cell (WBC) count as the best rapid-test indicator of possible occult bacteremia or other serious bacterial illness. Many primary care clinicians rued seeing a febrile but well-appearing 28- to 90-day-old infant with a WBC count barely over 15 000/mm^3 since the next recommended step was to order a lumbar puncture and empirical antibiotics. Experience had taught us that while this WBC cutoff value had a high negative predictive value, it also had a very low positive predictive value given the rarity of serious bacterial infection. While we didn't want to miss treating the rare case of serious bacterial infection, we knew that most of these infants would be just fine without our intervention.

The widespread accessibility of rapid CRP testing and increasing availability of timely procalcitonin results have rendered this diagnostic dilemma obsolete. Ordering these tests when confronted with a febrile infant can save clinicians, our patients, and our patients' families undue stress. At the same time, even though CRP is a better indicator than WBC of invasive bacterial disease, laboratory tests still cannot replace sound clinical intuition. Inflammatory marker testing should be adjunctive to clinical reasoning and ordered thoughtfully to minimize false-positive results and ensure responsible health care-cost stewardship.

Linda Y. Fu, MD, MS
Associate Editor, In Brief

Acknowledgments
Thank you to Dr Anita Dhanrajani for her review of this article.

VISUAL DIAGNOSIS

Multiple Painless Papules in the Oral Cavity of a 4-Year-Old Boy

Victor N. Oboli, MD,[1] Dyuti Kumar,[2] Blessing Adanda Chuku, MD,[3] Magda Mendez, MD[3]

[1]Section of Pediatric Emergency Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut
[2]St. George's University, School of Medicine, Grenada, West Indies
[3]Department of Pediatrics, New York City Health + Hospitals/Lincoln Medical Center, Bronx, New York

PRESENTATION

A previously healthy 4-year-old boy who emigrated from Brazil presents to the pediatric clinic with his parents for a health maintenance visit. The parents are concerned about oral lesions that have persisted for 8 months. The parents deny food or medication allergies, weight loss, history of bleeding from the lesions, chronic medication use, trauma, pain, fever, or difficulty swallowing. His immunizations are up to date. Before this well-child visit, he was seen at an urgent care center 2 months earlier for the same lesions, and the parents were given reassurance without immediate interventions. There has been no significant increase in the size of the lesions since onset. Vital signs on arrival were as follows: temperature, 99.7 °F (37.6 °C); heart rate, 104 beats/min; respiratory rate, 21 breaths/min; blood pressure, 102/70 mm Hg; and oxygen saturation in room air, 99%. His body mass index is at the 67th percentile. The physical examination is pertinent for several nontender, whitish-pink papules on the inner buccal mucosa (Figure 1), inner lower lip (Figure 2), and lateral sides of the tongue (Figure 3) and enlarged circumvallate papillae on the posterior third of the tongue (Figure 4). The lesions are firm to palpation, nontender, and not scrapable. He has no skin lesions on examination. The patient is referred to a dentist and oral medicine specialist for further evaluation. The patient's history and examination findings confirm the diagnosis.

DIAGNOSIS

A diagnosis of focal epithelial hyperplasia (FEH, also called Heck disease) was established. Several oral mucosal disorders, such as oral hairy leukoplakia, Peutz-Jeghers syndrome, verruciform xanthoma, and verrucous carcinoma, can mimic this condition.

DISCUSSION

FEH, also known as Heck disease or multiple FEH, is a rare and benign oral pathology characterized by the appearance of 1 or more lesions on the inner lining of the oral cavity. It results from the proliferation of the epithelial cells in the affected area.[1] While FEH is encountered in immunocompromised individuals and populations living with HIV, it is rare, with a prevalence of less than 2%, and it can also occur in individuals who are not immunosuppressed. It is more common among Indigenous populations, particularly Native Americans, South Americans, and Inuit and Yupik populations.[1–4] Certain nononcogenic strains of human papillomavirus (HPV),

AUTHOR DISCLOSURE: Drs Oboli, Kumar, Chuku, and Mendez have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

PREVIOUS PRESENTATION: This case was presented at the PEMPix Finalist Case Competition, Section on Emergency Medicine, American Academy of Pediatrics National Conference and Exhibition (October 2023, Washington DC).



FIGURE 1. Multiple whitish-pink and raised papules on the left inner buccal mucosa of the oral cavity.

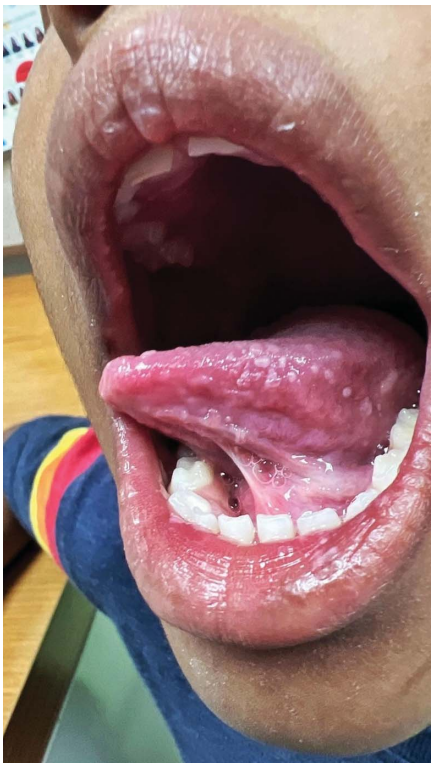


FIGURE 3. White-colored papules on the left lateral surface of the anterior two-thirds of the tongue.



FIGURE 2. Widespread, white-colored papules on the inner lining of the lower lip.



FIGURE 4. Enlarged, fleshy, and hyperemic circumvallate papillae on the posterior third of the tongue.

specifically HPV-13 and HPV-32, have been associated with FEH and are transmitted through salivary contact of infected persons.[1,2,4] These viruses can trigger the development and propagation of FEH lesions. A systematic review by Sethi et al of cases published from 1966 to 2020 reported that patients affected by FEH were aged 3 to 92 years, with an average age of 23.1 years. Females are most affected, with a male-to-female ratio of 3:4.[2]

Lesions can present in 2 forms: papulonodular and papillomatous. The former is characterized by a raised, pink, and "smooth" appearance, while the latter exhibits a cobblestone-like texture.[3] These lesions may present as single or multiple spots and can vary in color, ranging from near-white to mucosa-colored. They may be flat or raised, measuring 0.2 to 3 cm in diameter.[4] In addition, lesions are typically painless and do not cause any discomfort; however, in some cases, the lesions are associated with pruritus or a burning sensation and, rarely, dysphagia. They are commonly seen on the buccal mucosa, lower lip, and commissures (the corners of the mouth). However, there have been reports of lesions on the upper lip, tongue, hard palate, and gingiva.[1,5]

The diagnosis of FEH is typically clinical. Diagnosis is based on clinical presentation, history, and physical examination of the lesions. Extensive laboratory investigations are not required except in cases of uncertain clinical presentations or diagnoses. Patients can be referred to oral medicine specialists (dentists specializing in disorders of the orofacial region) for further evaluation if the diagnosis is uncertain. While histopathology of biopsied lesions may confirm the diagnosis and is considered the gold standard to exclude other oral pathologies, it provides little to no therapeutic benefit, as lesions heal spontaneously over time without acute interventions or malignant progression.[2] Studies are lacking to describe the expected time to resolution of FEH lesions. Histological features of FEH include parakeratosis, widened and thickened rete ridges, and ballooning degeneration. Koilocytes with clear cytoplasm and inclusion bodies are associated with HPV-related conditions. Tissue sections can also show cells with "mitosoid" and fragmented nuclei resembling mitotic figures. Polymerase chain reaction analysis can aid in detecting HPV DNA, but it is not diagnostic of FEH. Moreover, testing for HPV infection is rarely performed in patients with FEH, as it does not alter treatment decisions or outcomes.[4]

FEH usually resolves spontaneously, leaving no residual effects, but there have been cases where lesions have persisted for over 30 years.[1] Although FEH requires no acute interventions, some treatment options include topical 5% imiquimod, cryotherapy, cauterization, surgical resection, laser excision, and topical 80% trichloroacetic acid. Research on the prevalence and implications of HPV infections in patients with FEH, particularly in the pediatric population, is limited. Nonetheless, routine HPV vaccinations should be administered at the recommended ages.

Differential diagnoses to consider include oral hairy leukoplakia (manifests as whitish corrugated lesions on the tongue, usually triggered by Epstein-Barr virus), Peutz-Jeghers syndrome (hyperpigmented macules or spots on the tongue/oral mucosa associated with gastrointestinal polyps), verruciform xanthoma (mostly isolated and solitary cauliflower-like lesion with a rough/pebble surface), and oral squamous cell carcinoma (sore, lump, or ulcer on the oral cavity with variable presentations and symptoms).

PATIENT COURSE

The parents received reassurance and counseling from the oral medicine specialist regarding the expected outcome of the condition. Our patient was scheduled for a 6-month follow-up to reevaluate his oral lesions and for a possible biopsy and treatment if the lesions persisted or if the parents desired treatment. He remained asymptomatic and was growing and developing well, and during the 6-month follow-up visit, the lesions had nearly entirely resolved. He was then discharged from the oral medicine clinic and advised to follow up with his primary care pediatrician.

Summary

- FEH is a benign oral condition characterized by 1 or more lesions on the inner lining of the mouth due to the overgrowth of the epithelial cells in the affected area.
- It is essential for pediatricians to have knowledge about FEH and be able to educate and reassure parents about its benign nature despite its rarity.
- FEH has been linked to certain HPV strains; however, routine screening is not required, as it doesn't alter treatment decisions or outcomes. Regardless, patients should be vaccinated against HPV at the appropriate ages.
- The condition is self-limiting with spontaneous regression, and treatment is unnecessary except for persistent or symptomatic lesions. Treatment can also be offered for cosmetic and psychological reasons.
- Treatment options include topical 5% imiquimod, cryotherapy, cauterization, surgical or laser excision, and topical 80% trichloroacetic acid.

Acknowledgments

Thank you to Professor Muhammad Waseem for his review of the manuscript.

References for this article can be found at
https://doi.org/10.1542/pir.2024-006550