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**Update in the Diagnosis and
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Use of the 20-Valent
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**Monoclonal Antibody
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Visual Diagnosis

**10 Going on 2: A Case of Short
Stature in an Immigrant Child**



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Headache Care

Sara Pavitt, MD, Samantha L Irwin, MB, BCh, BAO, FRCPC

Dell Medical School, The University of Texas at Austin, Austin, Texas

EDUCATION GAP

Headache is the most common neurological symptom presenting across health care settings in children and adolescents. However, there is often uncertainty in delineating a primary from a secondary headache disorder and initiating an appropriate workup. Additionally, new treatment strategies within headache medicine have been rapidly emerging and are changing the landscape of headache management.

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

1. Differentiate and aid in the identification and diagnosis of primary vs secondary headache disorders.
2. List pediatric red flags associated with secondary headache disorders.
3. Outline when to pursue further medical investigations.
4. Design acute and preventive treatment tool kits for primary headache disorders.

ABSTRACT

Primary headache disorders are common within the pediatric population and often lead to disruption in multiple areas of life. It is important to systematically approach patients presenting for the evaluation of headaches to determine if the symptoms originate from a primary or secondary headache disorder. Once a diagnosis is established, patients should be offered treatment to adequately address the headache disorder. Over the last 6 years, multiple new treatment options have emerged, with growing selections available for children and adolescents. In this review, we discuss the evaluation, diagnosis, and treatment approach to primary headache disorders.

HEADACHE HISTORY AND EXAMINATION

The initial evaluation of a patient presenting with a headache should focus on delineating a primary from a secondary headache disorder. Primary headache disorders are disease states in which headache is the primary symptom, such as migraine or tension-type headache. Secondary headache disorders occur when a headache is caused by another disorder, such as obstructive sleep apnea, anemia, or visual refractive errors. Making this differentiation starts by creating a comfortable environment with the expectation that the appointment will be spent discussing headaches. Sitting the child closest to the examiner encourages direct communication with

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ABBREVIATIONS

CBT	cognitive behavioral therapy
CGRP	calcitonin gene-related peptide
CM	chronic migraine
CSF	cerebrospinal fluid
CT	computed tomography
eCONTS	external combined occipital and trigeminal nerve stimulator
EM	episodic migraine
eTNS	external trigeminal nerve stimulator
FDA	Food and Drug Administration
ICHD	International Classification of Headache Disorders
IIH	idiopathic intracranial hypertension
MR	magnetic resonance
niVNS	noninvasive vagal nerve stimulator
NSAID	nonsteroidal anti-inflammatory drug
REN	remote electrical neuromodulation
SMART	Sleep, Meals, Activity, Relaxation, Triggers
SNOP3Y	Systemic disease, Neurologic disease, Onset, Occipital, Progressive, Positional, Precipitated by Valsalva, Young age
sTMS	single pulse transcranial magnetic stimulation

TABLE 1. SNOP3Y Mnemonic Outlining Red Flags for a Secondary Cause of Headaches in Pediatric Patients

Red Flag	Potential Association
Systemic disease signs/symptoms	Systemic conditions associated with headaches, including rheumatologic disorders, endocrine disorders, pregnancy, and infectious diseases
Neurological disease signs/symptoms	Underlying intracranial process driving the headache
Onset sudden (thunderclap headache) or onset in sleep	Subarachnoid hemorrhage or increased intracranial pressure
Occipital location	More common pain location for brain tumors; however, an abnormal neurological examination would also be expected if the headache is caused by a secondary cause
Progressive	Intracranial processes such as a brain tumor
Positional	Increased intracranial pressure (IIH or secondary cause) or low intracranial pressure (CSF leak)
Precipitated by Valsalva	Increased intracranial pressure, Chiari malformation
Young age (<6 y old)	Intracranial abnormality

Abbreviations: CSF, cerebral spinal fluid; IIH, idiopathic intracranial hypertension. Adapted from Sziperka.¹

the patient. When asking questions, the patient should be addressed directly, receiving input from the guardian when needed. Often, the child who is experiencing the headache will give different information from the guardian.

The headache history should include a focused set of questions assessing the headache and how it has changed over time. It is essential to ask about headache onset, frequency, timing of any temporal pattern changes, location, aggravating and alleviating symptoms, associated symptoms, and red flag features. The modified mnemonic SNOP3Y (Systemic disease, Neurologic disease, Onset, Occipital, Progressive, Positional, Precipitated by Valsalva, Young age)¹ (Table 1) can be used to aid in assessing red flags for secondary headache disorders.

Patients who present with signs or symptoms of systemic disease should have an expanded evaluation based on those findings. Up to 60% of pediatric patients who present to the emergency department for headache have a headache secondary to a viral illness such as influenza.² For patients presenting with weight gain and fatigue, thyroid studies should be considered, or a sleep study for patients with snoring, excessive daytime sleepiness, and headaches that start in the morning.

Patients often experience episodes of headache long before they present to medication attention. Therefore, it is important to understand when headaches started and

how they have changed over time. A headache that began abruptly and rapidly became daily and continuous over weeks is more concerning for a secondary headache disorder compared with episodes of headache that have increased in frequency over months to years. A headache disorder that has been occurring for more than 6 months without accumulation of additional neurological signs and symptoms is reassuring against a secondary cause.³

It is important to perform a complete general examination to assess for signs that may be associated with a systemic process that may be causing or contributing to the headache disorder. A neurocutaneous examination is critical in pediatrics because the brain and skin share an embryologic origin. A complete neurological examination, including fundoscopy, should always be obtained. Patients who have underlying brain abnormalities causing their headaches (eg, brain tumors) will likely have abnormalities on their neurological examination.^{2,4} Given that the posterior fossa is the most common place for brain tumors to occur in the pediatric population,⁵ special attention should be given to the cranial nerve, cerebellar, and fundoscopic examinations. If red flags are identified on history and/or abnormalities on the physical examination, brain imaging should be obtained. Magnetic resonance (MR) brain imaging with and without contrast is recommended over computed tomography (CT) to evaluate headache given the poor visualization of the posterior fossa with CT.⁶ In special circumstances, vessel imaging may also be warranted; for example, an MR venogram should be ordered if cerebral venous sinus thrombosis is suspected or a screening MR angiogram if a patient has 2 first-degree relatives with cerebral aneurysms.⁷ Serum studies should be obtained based on associated symptoms. For example, in patients with menorrhagia, a complete blood count and iron studies should be obtained to assess for iron deficiency. In those with fatigue and/or weight gain, thyroid studies should be considered. Additionally, in those with poor weight gain and/or diarrhea with headache, a celiac screen may be helpful. Table 2 lists disorders that have headaches as a common associated symptom.

EPIDEMIOLOGY AND IMPACT

The majority of children and adolescents will experience a primary headache event, with an estimated prevalence of 62% in children between the ages of 8 and 18 years.⁸ Migraine affects more than 1 billion people worldwide and is a leading cause of years lost to disability.⁹ The overall 1-year prevalence of migraine is approximately 12%, 7% of which are males and 17% of which are females.¹⁰ Prepuberty, male-to-female ratios are equal. It is common in the clinic

TABLE 2. Common Disorders That Have Headache as an Associated Symptom

Rheumatologic	Rheumatic fever, SLE, Behcets, Kawasaki, CNS vasculitis
Endocrine	Thyroid abnormalities, PCOS, diabetes, hypertension
Infectious disease	Systemic infections (viral, bacterial, fungal), meningitis
Toxic/metabolic	Ingestion, carbon monoxide poisoning, mitochondrial disorders such as MELAS, electrolyte disturbances
Allergy/immunology	Seasonal allergies
Hematology/oncology	Primary brain tumors, CNS metastasis, anemia, sickle cell disease
Vascular	Sinus venous thrombosis, ruptured vascular abnormality (AVM, cavernous malformation, aneurysm)
Neurologic	Epilepsy, demyelinating disorders, leukodystrophy, stroke, hydrocephalus, intracranial hypotension, autonomic dysfunction, idiopathic intracranial hypertension
Gastrointestinal	Celiac disease, irritable bowel syndrome
Pulmonology	Obstructive sleep apnea
Psychiatric	Mood disorders
Ophthalmology	Refractory errors, corneal injury, acute glaucoma

Abbreviations: AVM, arteriovenous malformation; CNS, central nervous system; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; PCOS, polycystic ovary syndrome; SLE, systemic lupus erythematosus.

to see boys and girls aged 8 years with migraine at an equal frequency.¹¹ Chronic migraine, defined by the International Classification of Headache Disorders (ICHD) third edition¹² as headache occurring 15 days a month or more for 3 months, with 8 of those days having migraine-associated features and/or believed by the patient to be a migraine or be relieved by migraine treatment (Table 3), occurs in approximately 0.6% of children aged 5 to 12 years, 1% of adolescents, and up to 2% of adults.^{10,13,14} Evolution from episodic to chronic migraine occurs in about 2.5% of people per year.¹³ However, reassuringly, 10% to 12% of patients per year can revert to episodic if adequately managed.^{15,16}

DIAGNOSIS

The diagnosis of primary and secondary headache disorders can be aided by the ICHD. Making the diagnosis requires careful history taking and a thorough examination. Per the ICHD-3 criteria, each diagnosis requires that it is “not better accounted for by another ICHD-3 diagnosis.” Table 3 lists common headache disorders encountered in the pediatric population.

Childhood Episodic Syndromes

“Episodic syndromes that may be associated with migraine” encompass various associated conditions that are seen with

greater frequency in those with a personal or family history of migraine or an increased likelihood of developing the condition, suggesting a relationship to early life migraine genetics. Inquiring about these syndromes can help increase diagnostic confidence for a primary headache disorder in an otherwise well-appearing child with a normal neurological examination. For all the episodic syndromes, generally speaking, at least 5 attacks should have occurred, and the child should be asymptomatic with a normal examination between attacks. The syndromes include, by order of typical age of onset, infantile colic (onset at age 1–3 months), benign paroxysmal torticollis of infancy (onset at age 4–6 months), alternating hemiplegia of childhood (onset around age 18 months), benign paroxysmal vertigo of childhood (onset around age 2–4 years), and recurrent gastrointestinal disturbance, which includes cyclic vomiting syndrome (onset around age 5 years) and abdominal migraine (onset around age 7 years). Motion sickness, cold-stimulus headaches, recurrent limb pain, periodic sleep disorders, and restless leg syndrome also seem to occur with greater frequency in those with migraine.

TREATMENT

Our discussion on treatment focuses on migraine; however, many experts will extrapolate these recommendations to other primary headache disorders, especially if there are migrainous features.

Although the diagnosis of migraine is centered on 4 major associated symptoms (photophobia, phonophobia, nausea, and vomiting), the clinical presentation and symptoms experienced by patients are heterogeneous. Therefore, it is important to create an individualized treatment plan for each patient that targets their specific needs and most bothersome symptoms, thereby minimizing the potential for significant disability due to the attack. Often, patients require a multimodal approach. Furthermore, it is important to diagnose and provide specific treatment of comorbid disorders that may be influencing the underlying headache disorder. Common comorbidities associated with migraine include sleep disorders such as insomnia and restless leg syndrome; mental health disorders, such as anxiety and depression; obesity; dysautonomic conditions such as postural orthostatic tachycardia syndrome; irritable bowel syndrome; and other pain conditions such as amplified musculoskeletal pain syndrome.

Broadly, there are 2 categories of migraine treatment: acute treatment and preventive treatment.

Acute treatment should be offered to all patients diagnosed with migraine.¹⁷ Treatment is most effective when

TABLE 3. Diagnosis of Headache Disorders Commonly Seen in Children and Adolescents

Diagnosis	Criteria	Notes
Tension headache	10 lifetime attacks Duration: 30 min to 7 d 2 out of 4 of: • Bilateral • Pressing/tightening • Mild/moderate • Not aggravated by activity Fulfill both of: 1. Only 1 of photophobia or phonophobia 2. Neither nausea nor vomiting	Types: • Infrequent e-TTH: less than 1 d per mo, less than 12 per year • Frequent e-TTH: 1 to 14 d per mo for more than 3 mo • Chronic TTH: more than 15 d per mo for more than 3 mo
Migraine	5 lifetime attacks Duration: 4 to 72 h in adults, 2 to 72 h in children and adolescents 2 out of 4 of: • Unilateral pain (often bilateral in children) • Pulsatile • Aggravated by movement (or avoidance of activity) • Moderate or severe pain level During the attack, at least 1 of: 1. Nausea and/or vomiting 2. Photophobia and phonophobia (can be inferred in children)	Chronic: more than 15 headache days per mo for 3 mo with 8 d having symptoms of migraine, believed to be migraine by the patient or responding to antimigraine therapy. For aura: at least 2 attacks with at least 1 of the following fully reversible symptoms: visual, sensory, or language symptoms • Motor aura is diagnosed as “hemiplegic migraine.” • Brainstem aura is called “migraine with brainstem aura.” It must be associated with at least 2 fully reversible brainstem symptoms (dysarthria, vertigo, tinnitus, hyperacusis, diplopia, ataxia, decreased LOC [GCS <13]) without motor or retinal symptoms • Retinal aura involves monocular visual changes. This is distinct from visual aura (bilateral visual field changes). Previously termed “ocular migraine.” Aura must have 3 out of 6 characteristics: 1. Gradual onset over 5 min 2. Two or more symptoms in succession 3. Each symptom lasting 5 to 60 min 4. At least 1 unilateral symptom 5. One positive symptom 6. Accompanied or followed within 60 min by headache Abrupt onset differentiates this condition. A history of increasing frequency of headaches prior to the abrupt onset of a new daily headache is often absent. More common in children. Viral trigger is present in up to 50%. Prior episodic headache history occurs in 33%. 30% improve in 3 to 4 mo. 80% improve in 2 y.
New daily persistent headache	Acute onset of headache within 24 h of a distinct and typically clearly recalled event; headache is unremitting, daily, and continuous for more than 3 mo. Phenotype often migrainous or tension-type. Can be self-limiting (remitting), relapsing-remitting, or persistent/refractory.	A history of increasing frequency of headaches prior to the abrupt onset of a new daily headache is often absent. More common in children. Viral trigger is present in up to 50%. Prior episodic headache history occurs in 33%. 30% improve in 3 to 4 mo. 80% improve in 2 y.

Abbreviations: e-TTH, episodic tension-type headache; GCS, Glasgow Coma Scale; LOC, loss of consciousness; TTH, tension-type headache. Trigeminal autonomic cephalalgias, cranial neuralgias, and posttraumatic headaches are additional headache disorders seen in the headache clinic that are not reviewed here.

started early in the migraine process at the onset of headache pain or even prior to the headache during the prodrome.^{18,19} In patients with migraine who experience nausea, a targeted anti-nausea treatment should also be provided, because nausea has been shown to be a strong predictor of school absences in people with migraine.^{17,20} Patients should trial a treatment strategy for at least 2 to 3 attacks before determining efficacy. Based on trial data, pain relief is generally experienced by about 60% of patients 2 hours after taking an acute abortive treatment, and pain freedom is experienced by 33% of patients by 2 hours.

Preventive strategies should be offered to all patients who experience 4 or more migraine attacks per month or to patients who have significant disability with their migraine

attacks.²¹ Most strategies take at least 8 weeks to assess efficacy. A pivotal clinical trial known as CHAMP assessed 2 prescription medications in the prevention of migraine and showed that although many children and adolescents improved, similar rates of improvement were seen in children taking either placebo or the medications.²² Therefore, starting an initial preventive strategy with a side effect profile similar to a placebo is preferable.²¹ The different strategies are outlined below.

Lifestyle Regulation

Although there is mixed evidence surrounding the extent to which lifestyle regularity affects migraine, it is generally believed to be beneficial in decreasing the overall burden of

TABLE 4. SMART Recommendations for Lifestyle-Targeted Regulation for Migraine Care

Recommendations	
Sleep	• Work to achieve adequate sleep for age^a • Encourage a regular sleep schedule • Optimize overall sleep quality
Meals	• Obesity has been linked to increased migraine frequency • Maintain a consistent meal schedule, and avoid meal skipping • Eat a healthy, balanced diet • Aim to drink half your body weight (in pounds) in ounces of water (120 lb = 60 oz of water)
Activity	• Inactivity is linked to obesity • Aim for 30 min of physical activity 5 d a wk • Limit screen time to 2 h per d
Relaxation	• Relaxation training such as mindfulness, deep breathing, and biofeedback may be helpful in reducing stress and anxiety
Triggers	• Keep a headache log to identify potential triggers, but remember triggers are often cumulative • Reduce exposure to consistent migraine triggers

^aSleep duration based on age per the American Academy of Sleep. Modified and adapted from American Headache Society's First Contact.²⁶

disease with limited adverse side effects.^{23–25} However, when discussing lifestyle with patients, it is imperative to use a shared decision-making approach that creates achievable goals and avoids blaming the patient for lifestyle dysregulation, because that can undermine the provider-patient relationship.

The mnemonic SMART (Sleep, Meals, Activity, Relaxation, Triggers) is often used to help frame the lifestyle components important in migraine (Table 4).²⁶

Behavioral Interventions

Behavioral interventions, specifically cognitive behavioral therapy (CBT), are beneficial as a monotherapy and, when added to a preventive medication, are superior to medication alone within the pediatric population.^{27,28} CBT is a defined, short-term course of treatment that involves bringing awareness and understanding around how emotions and thoughts intersect with physical symptoms. CBT involves learning how to modify cognition and behavior to aid in minimizing pain and disability. It is recommended that resources for pain-targeted CBT be offered to all patients who qualify for preventive treatment.²¹ However, given limitations in access to behavioral health providers, prioritizing patients with chronic headache disorders or disability associated with the headache disorder may be warranted.

Additional behavioral interventions that may reduce headache frequency and associated disability are biofeedback, mindfulness, and relaxation techniques.^{29–31} These strategies activate the parasympathetic nervous system to counteract the increase in sympathetic drive during migraine.

Physical Therapy

Physical therapy may play an important role in multidisciplinary headache treatment. Targeted treatment can be provided to address secondary headache conditions involving the head and neck such as temporomandibular joint disorders or cervicogenic headache, which may be the sole cause of headache or contributing to a primary headache disorder. There is also growing evidence that physical therapy can be an effective treatment of tension-type headaches and migraine without an associated secondary head and/or neck disorder.^{32,33} This therapy is typically individualized for each specific patient but often targets posture adjustments and stretching/strengthening the head and neck musculature.³⁴

MEDICATIONS

Acute Medications

Mild to moderate pain is typically treated with a nonsteroidal anti-inflammatory drug (NSAID), most commonly ibuprofen (10 mg/kg every 6 hours) or naproxen (10 mg/kg every 12 hours).³⁵ If NSAIDs are contraindicated, acetaminophen can also be used (15 mg/kg every 6 hours). It is important to ensure patients are receiving the correct weight-based dose prior to determining efficacy. For moderate to severe pain, patients should be offered a migraine-specific medication in addition to the NSAID. This is typically a triptan medication. Triptans approved in the pediatric population are listed in Table 5. Triptans are serotonin 5HT-1b, 5HT-1D, and 5HT-1F agonists. It is important to consider the route of administration and onset of action when determining which medication to start. For example, for patients who are unable to swallow pills, an oral dissolving tablet may be a good option. For patients who experience rapidly intensifying migraine, a nasal spray would likely be beneficial given its more rapid onset of action. If a trial of at least 2 triptans has been ineffective, one may consider off-label use of the class of medications known as the “gepants” (ubrogepant, rimegepant, and zavegepant) in patients without contraindications.

TABLE 5. Triptan Medications Approved in the Pediatric Population

Medication	Dose	Available Routes	Approval Age
Rizatriptan	5 mg, 10 mg	Tablet and oral dissolving tablet	6 y and older
Sumatriptan + naproxen	85 mg/500 mg 10 mg/60 mg	Tablet	12 y and older
Zolmitriptan	2.5 mg, 5 mg	Tablet, nasal spray	12 y and older
Almotriptan	6.25 mg, 12.5 mg	Tablet	12 y and older

Preventive Medications

There are multiple medication options for the prevention of migraine. Often, offering a patient a nutraceutical as a first-line preventive is recommended given the lower side effect profile. If 1 to 2 adequate trials of nutraceuticals have failed, prescription medications should be considered. The only medication approved by the Food and Drug Administration (FDA) for migraine in the pediatric population is topiramate for patients aged 12 years and older. There are no medications approved for children under the age of 12 years. Therefore, additional options are used off-label, with choices mirroring available medications in the adult population. A list of nutraceuticals (vitamins used as medicines) and commonly used prescription medications are listed in Table 6. We recommend using one medication at a time for a 3-month trial and discontinuing the medication if it is not beneficial to mitigate the possible side effects, pill burden, and polypharmacy.

Calcitonin Gene-Related Peptide Targeting Medications

Calcitonin gene-related peptide (CGRP) plays an important role in migraine pathophysiology. In adults, CGRP levels are elevated during a migraine attack and are elevated between attacks in patients with chronic migraine.³⁶ Preclinical studies support that CGRP elevation plays an integral role in initiating a downstream cascade involving the release of neuroinflammatory substances and vasodilation that lead to migraine symptoms.³⁷ In recent years, multiple medications blocking CGRP have become available. Although there are active clinical trials assessing the medications in the pediatric population,³⁸ currently, these medications are only approved for adults. Importantly, there has been a shift within the adult population to use these medications as first-line therapy.³⁹ Although there are no similar recommendations for children and adolescents, the American Headache Society does recommend considering these medications in patients over age 12 years with more

TABLE 6. Preventive Medication Treatment Options for Migraine in Pediatric Patients

Medication	Dosing Recommendations	Considerations	Medication Class
Nutraceuticals			
Magnesium	9 mg/kg/d nightly of elemental magnesium (typical dose is 400 mg if > 40 kg)	Diarrhea, soft stools, abdominal discomfort May improve anxiety, sleep, and constipation	
Riboflavin	100 mg to 200 mg twice daily	Orange urine discoloration	
Coenzyme Q10	100 mg to 300 mg daily	Increased belching May improve focus	
Melatonin	3 mg to 6 mg nightly	Sedation May improve sleep	
Prescription medications			
Amitriptyline	1 mg/kg/d nightly Max 150 mg/d	Sedation, weight gain, dry mouth, constipation, QT prolongation, increased urination, increased risk of suicidality	Tricyclic antidepressant
Nortriptyline	10 mg to 75 mg nightly Max 150 mg daily	Similar side effects to amitriptyline, but less severe	Tricyclic antidepressant
Venlafaxine	37.5 mg to 150 mg daily	Hypertension, tachycardia, insomnia, decreased appetite, increased sweating, mood changes, and suicidal thoughts	Serotonin-norepinephrine reuptake inhibitor
Topiramate ^a	2 to 3 mg/kg/d divided twice daily Max 200 mg daily	Cognitive slowing, word-finding difficulties, weight loss, paresthesia, kidney stones, glaucoma, decreased sweating	Antiepileptic
Propranolol	1–2 mg/kg/d divided twice or 3 times daily Max 120 mg/d	Hypotension, bradycardia; use caution in patients with asthma and diabetes	Beta-blocker
Candesartan ^a	4 mg to 16 mg daily	Hypotension, dizziness, angioedema, acute angle-closure glaucoma, acute myopia	Angiotensin II receptor blocker
Verapamil extended release	4 mg/kg/d Max 480 mg daily	Hypotension, dizziness, constipation, prolonged PR interval	Calcium channel blocker; may be helpful in hemiplegic migraine
Memantine	5 mg to 10 mg twice daily	Sedation, dizziness	NMDA-receptor antagonist
Cyproheptadine	0.25 mg/kg/d to 0.5 mg/kg/d Max 16 mg daily	Sedation, weight gain, sun sensitivity	Antihistamine

Abbreviations: NMDA, N-methyl-D-aspartate

^aTeratogenic.

TABLE 7. CGRP Medications**CGRP Monoclonal Antibodies**

Medication	Indication	Route	Available Dosing
Erenumab	Prevention in EM/CM	Sq injection	70 mg or 140 mg monthly
Fremanezumab	Prevention in EM/CM	Sq injection	225 mg monthly or 675 mg every 3 mo
Galcanezumab	Prevention in EM/CM	Sq injection	240 mg loading dose, then 120 mg monthly (some skip loading dose)
Eptinezumab	Prevention in EM/CM	IV infusion	100 mg or 300 mg every 3 mo
Gepants			
Rimegepant	Prevention and acute use in EM/CM	ODT	75 mg every other d for prevention Daily PRN acute
Atogepant	Prevention in EM/CM	Tablet	10 mg, 30 mg, or 60 mg daily
Ubrogepant	Acute use in EM	Tablet	50 mg or 100 mg daily PRN; can repeat dose after 2 h
Zavegepant	Acute use in EM	Nasal spray	10 mg daily PRN

Abbreviations: CM, chronic migraine; EM, episodic migraine; IV, intravenous; ODT, orally disintegrating tablet; PRN, as needed; Sq, subcutaneous.

than 8 headache days per month that cause disability after 2 previous preventives have failed (including nutraceuticals).⁴⁰ With this shifting therapeutic landscape, it is important to be familiar with these options as research evolves.

There are available monoclonal antibodies that bind to CGRP (ligand or receptor) and are approved for the preventive treatment of migraine. These large-molecule medications are delivered through subcutaneous injection (erenumab, eremanezumab, and galcanezumab) or intravenous infusion (eptinezumab). Gepants are small-molecule medications that block the CGRP receptor. They are approved for prevention (rimegepant, atogepant) and/or acute use (rimegepant, ubrogepant, and zavegepant) in migraine and are available in various routes of administration (oral or nasal). Table 7 outlines these medication options.

Medications that block CGRP should be avoided in patients with advanced liver or kidney disease, those with a history of stroke or intracranial vascular malformations, or those with a recent disruption to the blood-brain barrier (such as with active neuroinflammatory disease or active central nervous system infection). These medications should also be avoided in those with uncontrolled hypertension (erenumab) or Raynaud disease (all). The gepants should not be used in combination with strong CYP3A4 inhibitors.

NEUROMODULATION

Multiple devices now exist to manage migraine. Although some were initially indicated as acute treatment only, most are now offered with dual modalities and can be recommended to be used to treat attacks acutely or as a preventive strategy to reduce attack frequency and severity. Three devices have FDA clearance for use in adolescents: remote electrical neuromodulation (REN: Nerivio), single pulse transcranial magnetic stimulation (sTMS: eNeura), and noninvasive vagal nerve stimulator (niVNS: gammaCore). External trigeminal nerve stimulator (eTNS: Cefaly) and external combined occipital and trigeminal

nerve stimulator (eCOTNS: Relivion) are approved in patients aged 18 years old and older. Nerivio is a unique device that is applied to the upper arm and not the head, which is a beneficial feature for those with cranial allodynia (“pain due to a stimulus that normally does not provoke pain”). Treatment sessions are 45 minutes, and the mechanism is conditioned pain modulation, meaning a peripheral sensory stimulus triggers endogenous central descending pain inhibition to mitigate the symptoms of migraine. niVNS GammaCore looks similar to an ultrasound device and stimulates the vagal nerve. The sTMS device looks like a small book and delivers a painless magnetic impulse occipitally, mechanistically theorized to modify the occipital nerves and hypothalamus affecting cortical spreading depression, the hypothesized underlying mechanism for migraine aura. Benefits for all neuromodulation devices include the nontablet/nonmedicinal novel approach with a unique mechanism of action, fewer systemic side effects, and the absence of any risk for medication overuse. The devices can be used as monotherapy or an adjunct to pharmaceutical therapy in those with a high-frequency burden of headaches. Limitations to use include the typically high cost, poor or lack of insurance coverage, and the factors associated with requiring a physical device (storage, charging, travel/school logistics, etc).

REFERRAL TO NEUROLOGY

Typically, patients present to care when headaches are becoming frequent, disabling, and/or do not respond to over-the-counter pain medications. The first evaluation is usually with a primary care provider. If a patient does not have improvement after initiation of first-line acute and preventive therapy, a neurologic evaluation may be warranted. Furthermore, a neurology referral may be helpful if the headache symptoms are unusual, if a rare headache diagnosis is considered (for example, a trigeminal autonomic cephalgia), or if there are abnormal neurologic examination findings.

CONCLUSION

Headache is a common neurological symptom in the pediatric population. With a focused history and thorough physical examination, including neurological examination, primary from secondary headache disorders can often be delineated. When a primary headache disorder diagnosis is made, a patient-centered treatment plan should be given, because it may reduce the lifelong disability associated with the disorder. There are many emerging and novel treatment strategies within headache medicine that will likely become more widely available to children and adolescents in the near future.

Summary

- The evaluation of headache should include a detailed history and full physical examination including neurologic examination to guide the determination of the correct diagnosis.¹⁷ (Level of evidence: moderate + consensus)
- MR imaging is preferred over CT in the evaluation of headache.⁶ (Level of evidence: low + consensus)

- Patients with migraine should be offered an acute treatment plan with the goal of providing fast pain relief with limited side effects.^{17,35} (Level of evidence: strong)
- Patients with frequent migraine attacks or high disability attacks should be offered a preventive treatment plan.^{16,21} (Level of evidence: moderate + consensus)
- CBT combined with medication should be offered for preventive treatment.^{21,28} (Level of evidence: moderate)
- Migraine treatment often includes a multifaceted approach including disease education, lifestyle regulation, and trigger modification, along with specific acute and preventive treatment options.²¹ (Level of evidence: moderate)



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



1. A boy aged 10 years is brought to the clinic by his parents because of chronic headaches. His headaches began at the start of the prior school year. That year, the headaches occurred all around his head during half the school days but not usually on weekends. At that time, he did not complain of any associated light or sound sensitivity, vision changes, numbness or tingling, or weakness. The headaches improved over the summer, but at the beginning of this school year, the headaches returned. The headaches now occur in the front and top of his head most days. He denies any associated symptoms. Ibuprofen helps a little bit. His neurological examination results show mild wobbling when he walks heel to toe. His mother reports she had migraine at his age. The boy also reports ice cream headaches; there are no other medical problems. Which of the following history or physical examination findings is most likely an indication that this patient may have a secondary headache disorder?
 - A. Headache duration
 - B. Headache location
 - C. Headache response to medication
 - D. Ice cream headaches
 - E. Neurological examination
2. A girl aged 16 years is referred to the pediatrics clinic after her optometry examination showed bilateral papilledema. She reports increasing headaches for the past 2 months. There is associated light and sound sensitivity and nausea, and when the headaches are bad, she can have brief double vision. She denies vision loss, numbness, or weakness. Ibuprofen no longer helps. She has gained 6.8 kg in the past 3 months after starting oral contraceptives. Her mother and father have migraine, and her paternal uncle had a ruptured brain aneurysm at age 38 years. Her neurological examination results are normal. Which of the following is the most appropriate diagnostic test to perform on this patient?
 - A. CT of the brain
 - B. MRI of the brain
 - C. MRI and magnetic resonance angiography of the brain
 - D. MRI and magnetic resonance venography of the brain
 - E. No imaging studies
3. A girl aged 13 years is brought to the clinic by her parents because of migraine. Her headaches start with a feeling of malaise, then she gets a moderate headache with phonophobia and photophobia. She denies vision loss, nausea, vomiting, sensory symptoms, or weakness. Her migraine last several hours. Acetaminophen is ineffective; however, sleep helps. She is having migraine once or twice a week and has missed 2 days of school in the past month. In addition to anti-nausea treatment, it is recommended that this patient be started on non-steroidal anti-inflammatory drugs (NSAIDs). Which of the following treatment regimens for timing of starting NSAID treatment is expected to be most effective?
 - A. At the onset of headache
 - B. At the onset of vomiting
 - C. If there is no response to 24 hours of acetaminophen therapy
 - D. If vomiting persists despite anti-nausea treatment
 - E. In the prodrome phase prior to onset of headache

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4. A boy aged 15 years with asthma and attention-deficit/hyperactivity disorder (ADHD) is brought to the clinic by his parents because of chronic headaches for the past 2 years. He misses school 8 to 9 days a month due to headaches. He is taking ibuprofen most days but it does not help relieve the headaches. Daily magnesium helped but gave him diarrhea and daily coenzyme q10 was ineffective. Which of the following is the most appropriate treatment plan to be started for this patient?

- A. Daily riboflavin
- B. Daily riboflavin and topiramate with CBT
- C. Daily riboflavin with CBT
- D. Daily topiramate
- E. Daily topiramate with CBT

5. A girl aged 17 years with anxiety and depression, panic attacks, and ADHD has had migraine for 5 years. With improvement in sleep, stress management, and regular exercise, she is having 3 to 4 migraine a year. She takes fluoxetine, oral contraceptives, and methylphenidate. For acute treatment of migraine, ibuprofen has been ineffective. She tried sumatriptan tablet 1 time but it caused nausea and vomiting. Her mother asks about the new gepant class of medications for treatment of migraine. Which of the following treatment plans is the most appropriate next step to be recommended for this patient?

- A. Continue sumatriptan tablet for acute use for 2 to 3 trials
- B. Start rimegepant oral dissolving tablet for prevention
- C. Start rizatriptan oral dissolving tablet for acute use
- D. Start topiramate tablet for prevention
- E. Start upbrogepant tablet for acute use

Acute Otitis Media

Caroline R. Paul, MD,¹ John G. Frohna, MD, MPH²

¹Department of Pediatrics, NYU Grossman School of Medicine, NYU Langone Health, New York

²Department of Pediatrics, West Virginia School of Medicine-Charleston Division, Charleston Area Medical Center Institute for Academic Medicine, Charleston, West Virginia

EDUCATION GAP

There remains a gap in the implementation of the appropriate diagnostic criteria and management of acute otitis media.

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

1. List the diagnostic criteria for acute otitis media.
2. Discuss the therapeutic management of acute otitis media.
3. Describe the components of the pediatric otoscopic exam needed for the management of acute otitis media.
4. Describe the important role of the parent/caregiver in the diagnosis and the management of acute otitis media.

Acute otitis media (AOM) is the most common cause for antimicrobial treatment in young children, accounting for 56% of antimicrobial prescriptions for children aged 3 to 36 months and 40% of antimicrobial prescriptions for children aged 3 to 6 years.^{1,2} It is the second most common diagnosis after upper respiratory infection in children. The epidemiology of AOM has international and regional variances and has been impacted by both pneumococcal vaccines and the COVID-19 pandemic.^{3,4} Approximately 50% of children will have 1 episode of AOM by age 2 years, and by age 3 years, 80% will have had at least 1 episode.⁵

Health disparities have been noted in children with AOM.⁶ Children who are socially disadvantaged are less likely to receive treatment and more likely to experience complications of misdiagnosed and mismanaged episodes of AOM. Frequent ear infections have been associated with living below the poverty level. In under-resourced countries, chronic supportive otitis media is a leading cause of hearing loss.⁷

CLINICAL PRESENTATION

The most specific symptom of AOM is acute otalgia. This acute otalgia can manifest in many ways, from the acute onset of ear pain in the school-aged child to nighttime awakening, fussiness, and decreased appetite in younger children. While the acute otalgia is usually constant, it often appears to be worse in the evening. Fever can be associated with AOM but is not a consistent finding associated with AOM. Finally, recent or concurrent upper respiratory infection symptoms such as nasal congestion will often accompany the key symptoms of AOM.⁸

AUTHOR DISCLOSURE: Drs Paul and Frohna 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

AAP American Academy of Pediatrics
AOM acute otitis media
OME otitis media with effusion
TM tympanic membrane

EPIDEMIOLOGY

The peak incidence of AOM is between age 6 to 12 months. It is multifactorial in terms of risk factors, with males being at a slightly higher risk than females. Genetic predisposition, passive smoke exposure, conditions associated with decreased immunity, ciliary dysfunction, cochlear implants, daycare attendance, and family history of recurrent AOM in parents or siblings are other risk factors associated with AOM.²

AOM can be caused by viruses, bacteria, or a combination of both. Bacterial causes include the most common bacteria that occupy the upper respiratory tract: *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *Moraxella catarrhalis*. Since the implementation of conjugate pneumococcal vaccines, AOM is more commonly caused by nonvaccine serotypes. In terms of viral causes of AOM, the most common viral pathogens of otitis media include respiratory syncytial virus, adenovirus, influenza viruses, coronaviruses, human metapneumovirus, and picornaviruses. Infection with both viruses and bacteria is quite common, with one study documenting 66% coinfection rates.⁹

Many practicing clinicians likely noticed a significant decrease in the incidence of AOM during the COVID-19 pandemic. Several studies documented this decrease, along with a decrease in the use of antibiotics and emergency department visits for AOM.^{10,11} This decrease has largely been attributed to the social distancing and mask use that was in place during the pandemic. The incidence of other viral respiratory infections was also decreased during this time. The presence of SARS-CoV2 in patients with AOM has also been documented, suggesting that the 2 conditions can coexist.¹²

PATHOPHYSIOLOGY

AOM results from the acute inflammation of fluid in the middle ear space, which is dense with bacterial otopathogens. Many factors contribute to the acute inflammatory cycle, including bacterial persistence, viral infections, allergic rhinitis, recent or current upper respiratory infection, and anatomic variation and abnormalities, which set up the genesis of AOM.⁷ The eustachian tube is particularly essential in protecting the middle ear space from bacterial pathogens and viruses. A properly functioning eustachian tube is essential to the drainage of secretions. The eustachian tube also serves to equalize pressures. In young children under 2 years of age, the eustachian tube is less effective in these functions because it sits in a more horizontal position, leading to a slower drainage of secretions and allowing for more transmission of pathogens into the middle ear space.

DIAGNOSIS

The diagnosis of AOM rests on the visualization of the tympanic membrane and clinician competence in performing the overall ear exam.¹³ Therefore, it is important to understand the diagnostic criteria and to be proficient in performing the pediatric ear exam. The accurate diagnosis of AOM facilitates the appropriate usage of antimicrobial therapy for AOM. This also helps to mitigate the unnecessary use of antibiotics, thereby decreasing the overuse of antibiotics in general. Rising health care costs, increasing antibiotic resistance, and the possible need for surgical referrals for recurrent AOM stress the critical importance of an accurate diagnosis of AOM.

Understanding the anatomy of the middle ear is essential to making an accurate diagnosis of AOM. The middle ear is the area between the tympanic membrane (which separates the external and middle ear spaces) and the oval/round windows (which mark the beginning of the inner ear). The eustachian tube connects the upper respiratory tract to the middle ear and is more horizontal in infants and children. Several resources are available that physicians can use to explain to parents how AOM may arise in their child.¹⁴

When examining a normal tympanic membrane (TM), the membrane appears translucent, and the malleus is often seen through the TM in the anterior-superior quadrant (Figure 1). On the other hand, in cases of AOM, the diagnosis is dependent on a bulging TM (Figures 2 and 3). There is often decreased mobility of the TM, and the color is often erythematous with purulent and turbid fluid behind the membrane, suggestive of a bacterial infection.

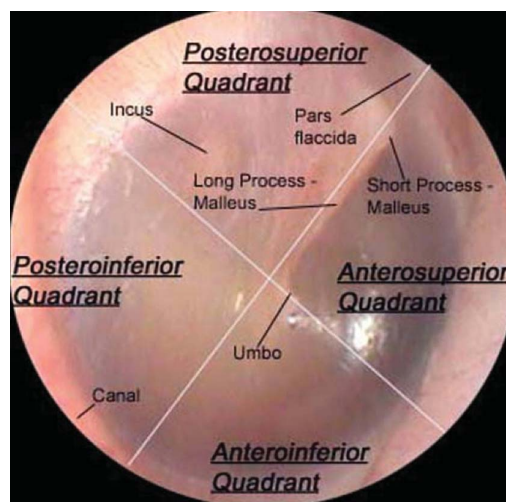


FIGURE 1. Visualization of the normal tympanic membrane. Image courtesy of ePROM.^{17,20}



FIGURE 2. Visualization of the tympanic membrane in a patient with acute otitis media. Image courtesy of ePROM.^{17,20}



FIGURE 4. Visualization of the tympanic membrane in a patient with otitis media with effusion. Image courtesy of ePROM.^{17,20}



FIGURE 3. Visualization of the tympanic membrane in a patient with acute otitis media. Image courtesy of ePROM.^{17,20}

Physical Examination

Training in pediatric otoscopy involves learning how to perform a proper ear exam in a child, which includes the use of appropriate techniques for holding and distracting a child, performing pneumatic otoscopy, and removing cerumen. A checklist (Table 1) containing the essential components of a pediatric ear exam has been shown to be helpful in teaching settings.^{15,16} It is important to remain proficient in pneumatic otoscopy and cerumen removal because it has been shown that these skills can decline over time.¹⁷

The examiner should perform a deliberate, stepwise exam. When performing the otoscopy exam, it is important to first determine the overall status of the patient, especially

with regards to age, development status, and the severity of their illness. This will guide the examiner's approach to the ear exam. Using an appropriate otoscope that provides adequate illumination and resolution to visualize the TM will allow the examiner to make a diagnosis of AOM. It is also important to use an otoscope that allows for the pneumatic otoscopy. Appropriately sized scope tips should be used based on the size of the child and the presence of any cranio-facial anomalies. In addition, other developmental needs of the child should be considered; for instance, some children may be afraid of the light from the otoscope, thinking that it may be hot or too bright for their eyes.

Next, the examiner should attend to the positioning of the patient. The school-aged child is likely to be on the examining table, and an otoscopy exam can generally be done with appropriate distraction and gentleness without the aid of a parent or caregiver. The younger child should be on the lap of the parent/caregiver or on the examining table with parent/caregiver assistance. Generally, infants younger than 9 months should be on the examining table in a supine position for a safe exam. An effective otoscopy exam does not necessarily require a lot of time. A "few golden minutes" should suffice in the absence of cerumen; during this time, the child is held in a comforting position that allows the examiner to perform a double-handed exam in which the nondominant hand is used to steady the head, and the dominant hand manipulates the otoscope to visualize the TM.

Once the examiner can see the anatomy, the examiner should take note of various characteristics of the TM, including the position of the TM, the color, presence of the bony landmarks, translucency of the TM, and any discharge.¹⁸

TABLE 1. Standardized Checklist for Otoscopy Performance Evaluation (SCOPE)¹⁵

GENERAL EXAMINATION^a
Discussion with caregiver
1. ☐ Yes ☐ No Discussed the need for otoscopic assessment
2. ☐ Yes ☐ No No Described the possible need to remove cerumen to view ear
3. ☐ Yes ☐ No Described positioning and the possible need for secure holding method
Equipment
4. ☐ Yes ☐ No Selected appropriate size ear speculum for proper seal and comfort to patient, given child's age/size Age____ Size____
Positioning
5. ☐ Yes ☐ No Ensured appropriate position (including caregiver assisted) for patient based on age and/or developmental status of patient
6. ☐ Yes ☐ No ☐ NA If needed, assured that child's head was appropriately secured
7. ☐ Yes ☐ No ☐ NA If not able to perform step 6, asked for assistance from caregiver
Distraction techniques
8. ☐ Yes ☐ No Used distraction techniques appropriate for age/development stage
Otoscopic examination
9. ☐ Yes ☐ No Inserted otoscope with dominant hand
10. ☐ Yes ☐ No Stabilized otoscope either by one-handed or two-handed method
11. ☐ Yes ☐ No Manipulated auricle to facilitate view of TM
12. ☐ Yes ☐ No Stabilized otoscope by bracing finger/dorsum of hand on infant/child's face or head
CERUMEN REMOVAL
13. ☐ Yes ☐ No Identified need for cerumen removal
14. ☐ Yes ☐ No Asked appropriately for assistance
15. ☐ Yes ☐ No Secured and/or distracted child prior to removal attempt
16. ☐ Yes ☐ No Stabilized head
17. ☐ Yes ☐ No Used scope appropriately to aid in removal of cerumen
18. ☐ Yes ☐ No Used appropriate instrument for removal
19. ☐ Yes ☐ No Able to remove some cerumen but inadequate for appropriate TM visualization
_____removed via direct visualization via open-headed otoscope
_____removed via indirect visualization
20. ☐ Yes ☐ No Appropriately identified that cerumen removal was inadequate for TM visualization
21. ☐ Yes ☐ No Able to remove adequate cerumen for appropriate visualization of TM
_____removed via direct visualization
_____removed via indirect visualization
PNEUMATIC OTOSCOPY
22. ☐ Yes ☐ No Appropriately attaches insufflators to otoscope
23. ☐ Yes ☐ No Uses appropriate speculum size: Age____ Size____
24. ☐ Yes ☐ No Checks for airtight seal
25. ☐ Yes ☐ No Use insufflator with patient appropriately
DIAGNOSIS

Abbreviations: NA, not applicable; TM, tympanic membrane

^aReprinted with permission

TABLE 2. Guidance for Parent and Caregiver Communication

Talking Points to Consider
1. Pain control: The common symptom of an acute middle ear infection is acute pain. Please discuss with your health care provider about pain management for your child.
2. Access to care: Ensure you have access to a health care provider in 24 to 72 hours after the diagnosis of an acute middle ear infection has been made.
3. Risk factors: Consider risk factors you can remove in your child's environment such as smoking.
4. Recognize that your provider cannot diagnose an ear infection without performing an ear exam on your child.
5. Know that antibiotics are not always needed; talk to your health care provider.
6. Seek care if your child is not getting better in 48 to 72 hours and sooner with acute and worsening symptoms.

Pneumatic otoscopy is an integral component of the overall pediatric ear exam. It allows for the visualization of the movement of the TM based on pressure changes. It is helpful in determining the presence of effusion in the middle ear space. Performing pneumatic otoscopy requires the examiner to be adept at the basic otoscopy skills described above. It involves attaching a bulb to the otoscope and then applying positive pressure (deflation of the bulb) and negative pressure (inflation of the bulb).

Many TM conditions can be associated with abnormal responses to positive and negative pressures. Most often, the reason for impaired mobility of the TM is due to effusion in the middle ear space. As AOM involves the accumulation of fluid in the middle space, impaired movement of the TM as determined by pneumatic otoscopy is associated with AOM. Still, pneumatic otoscopy does not differentiate between serous and purulent effusion. Importantly, it can also be the first step in the evaluation for other more concerning etiologies such as cholesteatoma. A child with impaired mobility of the TM as determined by pneumatic otoscopy should be followed closely.

The 2013 American Academy of Pediatrics (AAP) guideline provides a framework for the diagnosis of AOM.⁸ It is important to recognize that the bulging of the TM is required in each of these criteria in order to make the diagnosis of AOM. Below are excerpts from the AAP guideline regarding the diagnosis of AOM.

- “Statement 1A: Clinicians should diagnose acute otitis media (AOM) in children who present with moderate to severe bulging of the TM or new onset of otorrhea not due to acute otitis externa. Evidence Quality: Grade B. Strength: Recommendation.”
- “Statement 1B: Clinicians should diagnose AOM in children who present with mild bulging of the TM and recent (less than 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM. Evidence Quality: Grade C. Strength: Recommendation.”

Differential Diagnosis of AOM

Conditions such as otitis media with effusion (OME) (Figure 4), pharyngitis, and viral upper respiratory infection can mimic some of the symptoms of AOM. However, the acute onset of moderate to severe otalgia is not common with these other conditions. OME is often associated with abnormal findings of the TM such as air-fluid levels or a prominent short process of the malleus, mild otalgia, and often a sensation of ear fullness or popping when swallowing (Figure 3). With OME, there is no bulging of the TM or

other associated findings of acute inflammation of the middle ear effusions such as a purulent color of the TM. The management of OME is supportive and requires no medications. Still, OME must be followed up until resolution. It is important to document resolution of any abnormal TM finding so as to not overlook chronic OME or other conditions that might present initially in a similar manner such as a cholesteatoma. Of note, despite the distortion of the TM, OME does not represent an acute virulent bacterial infection of the middle ear fluid. Therefore, OME does not necessitate the use of antibiotics.

Chronic OME is defined as the persistence of middle ear effusion for more than 3 months. Evaluation by an otolaryngologist is recommended for children with unresolved OME and atypical symptoms accompanying OME such as concern for worsening hearing. Thus, it is important to be able to differentiate between the tympanic findings of OME and AOM, stressing again the importance of competency in the examination of the middle ear.^{13,19}

MANAGEMENT AND TREATMENT

The management and therapies discussed here will be broad based and follow evidence-based criteria. Pediatricians should consider the AAP guideline, studies published following the AAP guideline and the prevalence of pathogens in their community, and should adhere to a strict evidence-based approach in the treatment of their patient.⁸ It is vital that pediatricians continuously update their knowledge and skills regarding diagnostic criteria, epidemiology, and management plans. Online resources such as a peer-reviewed pediatric website offer the pediatrician access to rapid PubMed searches regarding current evidence-based therapeutic regimens.^{18,20} It is important to reference only peer-reviewed online resources.

Management Without Antimicrobial Therapy

Some patients with AOM can be safely managed without antimicrobial therapy. The natural history of the condition is such that the pain and discomfort will resolve after the first few days, and the use of antibiotics may result in 1 less day of symptoms. Safety-net antibiotic prescriptions and other similar protocols^{21,22} have been described, including in the AAP guideline, as a nonantimicrobial management protocol. Criteria for such management usually include older children with non-severe AOM (mild otalgia for less than 48 hours and temperature of less than 38.5°C), no other bacterial infection, and nontoxic status. These children can be followed closely without the use of antimicrobial therapy. Close follow-up is needed, and antibiotics should be started if signs

and symptoms worsen or do not improve over 48 to 72 hours. Current studies following publication of the AAP guideline do not support safety-net antibiotic prescriptions and other similar non-antibiotic treatment plans in an evidence-based manner for children younger than 2 years. Studies have shown that withholding antibiotics in children younger than 3 years can result in unfavorable outcomes.²³ Also, it is possible that many of the cases of AOM that resolved without antibiotics may have a viral etiology or may not actually have been AOM and rather were OME. This again calls for the need to be competent in the diagnosis of AOM and adhere to the diagnostic gold standard.

When managing patients with AOM, a key consideration is the control of pain, recognizing that the acute otalgia of AOM may resolve only after the first 48 hours of antimicrobial therapy. Appropriate nonprescription analgesic medication is the foundation of management of AOM in children. Oral acetaminophen or ibuprofen can be used to treat the otalgia. Aspirin should never be given for pain management. There is no evidence that pain caused by AOM is improved by alternating acetaminophen and ibuprofen in children,²⁴ and this regimen can lead to medication dosing errors. Otic drops for pain can be considered only after a patient has been examined and appropriately diagnosed. Otic drops are contraindicated in some conditions, including the presence or uncertainty of a ruptured TM.

Shared decision-making with families is appropriate in almost all cases of AOM. Indeed, educating the parent/caregiver about the diagnosis of AOM and the indications for antimicrobial treatment optimizes the overall management of AOM in the pediatric patient. Table 2 shows a script of talking points that can be used as a guide in the discussion and communication of managing AOM with a parent or caregiver. Additional resources including visual aids appropriate for parents are also available to help support parent/caregiver education about this condition.^{14,20,25}

Management with Antimicrobial Therapy

The AAP guideline recommends antibiotic therapy for bilateral AOM in children aged 6 to 23 months even if they do not have severe signs or symptoms;⁸ more recently, Wald has urged a similar approach (either treatment or close observation) to unilateral or bilateral AOM in younger children.²⁶ Clinicians will usually prescribe antibiotic therapy for children with severe signs or symptoms of AOM such as a temperature above 39°C, moderate to severe otalgia, or otalgia for at least 48 hours. The current AAP guideline recommends amoxicillin as first line of therapy for children who do not have an allergy to penicillin, have not been on penicillin in the past 30 days, and do not have purulent bilateral conjunctivitis.

It is recommended that antibiotics with beta-lactamase coverage for AOM should be prescribed if the patient has received amoxicillin in the past 30 days, has concurrent purulent conjunctivitis (suggesting *H influenzae* infection), and has a history of recurrent AOM unresponsive to amoxicillin or if one suspects *H influenzae* as the cause of AOM. Attention should be paid to local prevalence microbiology data as well.^{8,19}

Since the AAP guideline in 2013, well-regarded studies have emerged with recommended management regimens that differ from the guideline. Especially due to the impact of pneumococcal vaccines, there have been significant changes in the prevalence of microorganisms for AOM,²⁷ thus affecting the antimicrobial management of AOM in the pediatric patient. For instance, in 1999, *S pneumoniae* accounted for 40% to 45% of AOM, with *H influenza* (25% to 30%), *Moraxella catarrhalis* (15% to 20%), and *Strep pyogenes* (3% to 5%) following. In 2017, the pattern was *S pneumoniae* (15% to 25%), *H influenza* (50% to 60%), *M catarrhalis* (12% to 15%), and *S pyogenes* (3% to 5%). Overall, there has been a decrease in penicillin-resistant *S pneumonia*. Given these changes since the AAP guideline, Wald recommends a regimen with “regular dose amoxicillin-clavulanate as the preferred treatment (45 mg/kg/day in 2 divided doses of 400 mg/57 mg) for children with AOM” for 10 days to treat *H influenzae* and penicillin-sensitive *S pneumoniae* as initial therapy.²⁷ Pediatric clinicians should continue to monitor changes in microbial prevalence and resistance patterns to continue practicing in an evidence-based manner.

Variations in Duration of Antimicrobial Therapy. The AAP guideline recommends the traditional 10 days of antimicrobial treatment. Since the publication of the guideline, various studies have suggested that a 5- or 7-day course may be just as effective as the traditional 10-day course.²⁸ However, Hoberman et al demonstrated that a reduced duration of treatment with amoxicillin-clavulanate involving children aged 6 to 23 months with AOM was less effective.²³ Following the AAP guideline of 10 days of treatment, especially for younger children, seems most prudent currently.

Recommended Antimicrobial Agents. According to the current AAP guideline, unless the child has an anaphylactic reaction to penicillin, a course of 80–90 mg/kg/d of amoxicillin for 10 days is recommended. In the case of a non-type 1 allergic reaction, a cephalosporin such as cefdinir is recommended as first-line therapy.²⁹ Macrolides are not indicated in the treatment of AOM due to reported resistance. Further choices of antimicrobial treatment should be based on evidence-based guidance, community prevalence, and resistance patterns, with the advice of a pediatric infectious disease specialist as needed.

If the patient does not respond to amoxicillin in a timely manner, an agent such as amoxicillin/clavulanic acid should be prescribed to treat beta-lactamase-producing agents such as non-typeable *H influenzae*. Recent studies of the pharmacokinetics and pharmacodynamics of specific cephalosporins in respiratory infections suggest against the use of cefdinir in this scenario.^{29–31} Rather, intramuscular ceftriaxone should be considered. Most importantly, the patient who does not respond in a timely manner needs to be followed very closely. Access to medical care is important, and the parent/caregiver needs to be advised carefully as to indications for seeking further medical care, including persistent fever, acute changes in activity, otorrhea, and mastoid tenderness.

Management of Patients With Chronic OME

Using antibiotics for prophylaxis to prevent AOM is not indicated in pediatric patients.³² Referral to a pediatric otolaryngologist should be considered when AOM is not responding to standard antibiotics therapies in a timely manner, in children with complications of AOM such as mastoiditis, in children with underlying conditions that place them at risk for more invasive disease, and for patients with recurrent AOM (defined as 3 episodes in 6 months or 4 episodes in 1 year with 1 episode in the preceding 6 months).^{32,33}

Special Populations Aged 0 to 8 Weeks

Infants younger than 8 weeks diagnosed with AOM should be considered higher risk for atypical and severe disease. Pathogens at this age vary from other age groups; group B strep, gram-negative enteric organisms, and *Chlamydia trachomatis* should be considered. Febrile neonates with AOM should be considered for a full sepsis evaluation. In these high-risk groups, consultation with a pediatric infectious disease specialist can be helpful.

Complications

Early diagnosis and management of AOM is important because if it is left untreated, more serious complications can occur. In some cases, the infection can spread to the surrounding tissues and cause mastoiditis, which can be very painful and require surgical treatment. Another major complication, although less common, is meningitis. AOM can also cause the eardrum to perforate, leading to drainage of fluid from the ear. In rare cases, AOM can lead to hearing loss, which can have long-term effects on a child's development and ability to learn.

Primary and Secondary Prevention

Pediatricians should recognize the preventable risk factors of AOM. Breastfeeding in the first 6 months of life has been shown to be protective against AOM.^{34,35} In addition to

stressing the avoidance of tobacco smoke, pediatricians should encourage the annual influenza vaccination along with the age-appropriate administration of the pneumococcal vaccine as preventive measures for AOM.

Summary

- The diagnostic criteria for AOM require the presence of a bulging TM; there can also be decreased mobility of the TM, with an erythematous color and/or evidence of purulent, turbid middle ear fluid. The presence of fever and an erythematous TM alone is not diagnostic of AOM.⁸ (Strength of Recommendation: Strong)
- The management of AOM in children includes pain management and other supportive therapy. In some circumstances, a wait-and-see approach in which the patient is managed without antibiotics and the caregivers are provided with a prescription for antibiotics and criteria for use may be appropriate.^{8,21} (Strength of Recommendation: Moderate)
- The first-line treatment in patients not allergic to penicillin is a 10-day course of 80 to 90 mg/kg/d of amoxicillin. Further choices of antimicrobial treatment should be based on evidence-based guidance, community prevalence, and resistance patterns, with the advice of a pediatric infectious disease specialist as needed.⁸ (Strength of Recommendation: Strong)
- Competency in the pediatric ear exam, which includes the general approach, visualization of the TM, pneumatic otoscopy, and cerumen removal, is critical to the appropriate diagnosis of AOM.^{8,15} (Strength of Recommendation: Strong)
- Engaging the parents or caregivers in shared decision-making is important for patients with AOM. Supportive measures including the use of antipyretics, and indications for follow-up should be discussed with the parents and caregivers.^{14,20} (Strength of Recommendation: Moderate)



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



1. A 19-month-old boy is brought to the clinic by his parents because they noticed him to be fussy and pulling at his right ear. He attends daycare, and he has had multiple ear infections since he started daycare, which were treated with antibiotics. He was born at 34 weeks gestation to a G10 mother with no perinatal complications. His immunizations are up to date for his age. His height and weight are at the fifth percentile, and his head circumference is at the seventh percentile. His growth rate and development have been normal, and parents are both 5' 6" tall. The father smokes cigarettes mostly outside. There is no family history of allergies. There is a pet parrot in the household. In addition to daycare attendance, which of the following is an additional risk factor that most likely predisposes this patient to recurrent acute otitis media episodes?
 - A. Borderline prematurity
 - B. Having a parrot as a pet
 - C. Having no older siblings at home
 - D. Low mid-parental height
 - E. Passive smoking exposure
2. The patient in the above vignette was diagnosed on physical examination with right purulent otitis media. Among the following pathogens, which is the most likely cause of acute otitis media in this patient?
 - A. *Hemophilus influenzae*
 - B. Nonvaccine serotypes of *Streptococcus pneumoniae*
 - C. Respiratory viruses
 - D. *Staphylococcus aureus*
 - E. *Streptococcus pyogenes*
3. A 3-year-old girl is brought to the clinic by her parents because of a 2-day history of rhinorrhea and fever. This morning, she started to complain of a left earache and has had a decrease in activity and appetite. There are sick contacts in daycare. The patient is otherwise healthy. She takes no medications and is up to date on her immunizations. There are no known drug allergies and no previous history of recent illnesses. Physical examination shows red tympanic membranes with poor mobility bilaterally on insufflation (more so on the left than the right). Which of the following is the most appropriate antibiotic regimen in this patient?
 - A. Azithromycin 10 mg/kg on day 1 then 5 mg/kg on days 2–5
 - B. Amoxicillin 90 mg/kg/d for 7 days
 - C. Amoxicillin 90 mg/kg/d for 10 days
 - D. Amoxicillin-clavulanic acid 90 mg/kg/d for 7 days
 - E. Amoxicillin-clavulanic acid 90 mg/kg/d for 10 days

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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.



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4. A 2-year-old boy is brought to the clinic by his parents because of a 2-day history of high fevers up to 39°C associated with clear rhinorrhea, fussiness, bilateral redness of the eyes, decreased activity, and decreased appetite. He has had recurrent episodes of otitis media for the past 12 months since he started daycare for which he has been on multiple antibiotic courses. His immunizations are delayed due to "being sick all the time in the past year." His last vaccines were given when aged 12 months. He is diagnosed with bilateral otitis and conjunctivitis. The parents are reluctant to start another antibiotics course. The clinician explains to the parents that, if untreated, otitis media can lead to serious potential complications. Among the following, which is the most common potential acute complication of untreated otitis media in this child?
- A. Acute mastoiditis
 - B. Epidural abscess
 - C. Lateral sinus thrombosis
 - D. Meningitis
 - E. Stroke
5. In children who are diagnosed with recurrent episodes of otitis media, which of the following is the most likely potential long-term complication of recurrent acute otitis media that can affect a child's development and ability to learn?
- A. Acute perforation of tympanic membrane
 - B. Development of cholesteatomas
 - C. Episodes of acute otalgia
 - D. Fluctuating or persistent hearing loss
 - E. Mastoiditis

Update in the Diagnosis and Treatment of Tuberculosis in Children

Ana M. Alvarez, MD,^{1,2,3} Mobeen H. Rathore, MD^{1,2,3}

¹University of Florida Center for HIV/AIDS Research, Education and Service (UF CARES), Jacksonville, Florida

²University of Florida College of Medicine – Jacksonville, Jacksonville, Florida

³Wolfson Children's Hospital, Jacksonville, Florida

EDUCATION GAP

Data from clinical and epidemiological studies have led to several new recommendations in the areas of diagnosis and treatment of pediatric tuberculosis in the past few years. Due to the low incidence of tuberculosis in the United States, many primary care providers may not be familiar with these new recommendations.

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

1. List the risk factors for tuberculosis (TB) in children in order to decide when further evaluation is required.
2. Describe the difference between tuberculosis infection (TBI) and tuberculosis disease and identify the workup for each one.
3. List the advantages and limitations of tests for TB infection and become familiar with the new recommendations for these tests.
4. Identify the new preferred regimens recommended for TB infection in children.
5. Describe the principles of therapy for TB disease, including treating multidrug-resistant TB and recognizing the most commonly used drugs and the new options for shorter duration of therapy.

INTRODUCTION

In the last decade, there have been many advances in the diagnosis of tuberculosis (TB), and for the first time in more than 5 decades, new drugs have been developed and others have been repurposed for the treatment of TB, including multidrug-resistant TB (MDR-TB). These developments have made TB treatment easier and shorter. Still, TB was the world's second leading cause of death from an infectious agent, after COVID-19, with 1.3 million deaths in 2022. An estimated 10.6 million people developed TB in 2022 (including 410 000 with MDR-TB), with a global incidence of 133 cases/100 000 population.¹ It has been estimated that approximately 1.7 billion people worldwide have asymptomatic TB infection, including nearly 100 million children.² In the United States, there were 8331 reported cases of TB disease, with an incidence rate of 2.5 cases/100 000 persons in 2022.³ Given the low

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This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

AAP	American Academy of Pediatrics
AFB	acid-fast bacilli
BCG	Bacille Calmette-Guérin (TB vaccine)
BPaL	bedaquiline, pretomanid, and linezolid
BPaLM	bedaquiline, pretomanid, linezolid, and moxifloxacin
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
DOT	directly observed therapy
CSF	cerebrospinal fluid
CXR	chest x-ray
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
FDA	Food and Drug Administration
HRZE	isoniazid, rifampin, pyrazinamide, and ethambutol
HPMZ	isoniazid, rifapentine, moxifloxacin, and pyrazinamide
IFN- γ	interferon gamma
IGRA	interferon- γ release assay
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
MTB	<i>Mycobacterium tuberculosis</i>
NAAT	nucleic acid amplification test
Pre-XDR-TB	pre-extensively drug-resistant tuberculosis
QFT	QuantiFERON-TB Gold Plus (an IGRA)
TBI	tuberculosis infection
TST	tuberculin skin test

T-Spot	T-SPOT.TB test (an IGRA)
XDR-TB	extensively drug-resistant tuberculosis
Xpert	GeneXpert MTB/RIF
WHO	World Health Organization

ABBREVIATIONS OF TB MEDICATIONS

BDQ or B	bedaquiline
CFZ	clofazimine
CS	cycloserine
DLM	delamanid
EMB	ethambutol
ETA	ethionamide
FQ	fluoroquinolones
INH or H	isoniazid
LZD or L	linezolid
LFX	levofloxacin
MFX or M	moxifloxacin
MPM	meropenem
RPT or P	rifapentine
Pa	pretomanid
PAS	P-aminosalicylic acid
RIF or R	rifampicin
PZA or Z	pyrazinamide

incidence in the United States, many pediatricians are not familiar with the new advances in the management of TB in children.

PATHOGENESIS

Transmission of TB is mostly airborne and requires exposure to contagious adults or adolescents with active pulmonary (or laryngeal) TB, who actively cough. The factors that affect transmission are the susceptibility of the exposed person, the infectiousness of the person that has TB, proximity and duration of exposure, and environmental factors, such as poor air circulation, secondhand smoke, household crowding, and indoor wood-burning stoves.^{4,5} People with cavitary TB are usually more contagious than those with nodular TB. Children aged younger than 10 years are usually not contagious because they most commonly have paucibacillary disease (ie, affected lymph nodes and lung infiltrates have a low bacterial load), and they do not have the force to expel the organisms in droplet nuclei. The most important risk factor for TB in children is being a household contact of an active case.⁶ Other risk factors include place of birth, travel, residence or exposure to persons in countries that are endemic for TB, including countries from Africa, Asia, the Middle East, the former Soviet Union, and Latin America, and, to a lesser extent, exposure to individuals that experience homelessness, use illegal drugs, or have been residents of correctional facilities or other congregate settings.⁷

After inhalation of *Mycobacterium tuberculosis* (MTB) droplet nuclei, the establishment of the infection depends

on the level of efficiency of the clearance mechanisms of the airway, the innate immune system (phagocytosis and killing by alveolar macrophages), and the adaptive immune system (formation of granuloma, which undergoes caseous necrosis, encapsulation, fibrosis, and/or calcification).^{4,8} These processes can control TB infection in most cases. However, some organisms can survive in the granuloma for many years. This stage is generally called “latent tuberculosis infection” (LTBI) or, preferably, “tuberculosis infection” (TBI). In some children, hilar or paratracheal lymph nodes become enlarged by the inflammatory reaction to the tubercle bacilli, sometimes causing a partial obstruction of the airway, which can lead to hyperinflation, collapse of distal segments of the lung, and secondary bacterial pneumonia. Inflamed, caseous nodes may erode the bronchial wall, causing endobronchial TB.⁶

When the infection is not controlled by the adaptive immune system, the bacilli are not contained in the granuloma and they spread via the bloodstream or via the lymphatic system to the lungs (pulmonary TB), distant organs (extrapulmonary TB), or multiple organ systems (disseminated TB).⁸ Spread can occur soon after the primary infection or years later (reactivation of a latent infection), and it is more common in the immunocompromised patient. In children, primary disease is more common than reactivation, but adolescents can present with reactivation.⁶

Other forms of transmission include cutaneous, via ingestion of unpasteurized dairy products (*M bovis*), and vertical (congenital), but these forms of transmission are rare.⁶

CLINICAL ASPECTS

TB Infection

TB infection is defined by having a positive test for TBI, a normal chest x-ray (CXR), and no symptoms or abnormal findings on physical examination suggestive of TB disease. Most children are asymptomatic when they acquire primary TBI. A few children have mild to moderate signs and symptoms such as fever, cough, and malaise occurring a few weeks prior to testing positive for TBI and resolving within 5 to 7 days without specific treatment.

The risk of advancing from TBI to TB disease is approximately 10% in the general population. However, the risk is higher in the first 2 years after the primary infection. It is estimated that 75% of patients with TB disease develop it within 1 year of contact with an index case and 97% within 2 years after exposure.⁹ If not treated for TBI, the estimated 2-year risk for developing TB disease is 19% in children younger than 5 years. Of the children that develop TB disease, 83% are diagnosed within the first 3 months of their known exposure.¹⁰

Pulmonary TB

This is the most common form of TB disease, accounting for approximately 80% of cases. The clinical presentation can be deceptive and varies among different age groups. Infants usually present with symptoms such as dry cough and wheezing secondary to airway obstruction due to external compression or internal narrowing of the airway due to endobronchial disease. Affected infants also usually have fever and weight stunting. On the other hand, school-aged children may be asymptomatic or may have mild cough with or without fever. The CXR typically shows perihilar lymphadenopathy with or without an associated infiltrate or atelectasis. Many children in this age group are discovered only via active contact investigation. A few patients at this age present with a clinical picture suggestive of bacterial pneumonia with signs of respiratory distress and a high fever. The CXR may show lobar infiltrates with or without significant pleural effusion. Adolescents more commonly present with the classic symptoms of prolonged fever, chronic productive cough, night sweats, and weight loss. Their CXR findings may be similar to those of school-aged children, but the CXR may show cavitation in the upper lobes similar to what is seen in adult patients.

Extrapulmonary TB

This form of TB can occur in almost any organ system, including superficial and visceral lymph nodes and the central nervous, gastrointestinal, osteoarticular, and genitourinary systems. The most common sites are the peripheral lymph nodes in the cervical region. The most severe form of extrapulmonary TB is meningitis, which occurs in only 0.5% to 2% of TBI cases, but it is important to recognize early because the prognosis relates in great part to the time of initiation of treatment. TB meningitis occurs more often in children younger than 2 years and in immunocompromised hosts.

Miliary or Disseminated TB

In miliary or disseminated TB, there is involvement of 2 or more organ systems. The clinical picture is often indolent, but it may be acute with fast progression. Early pulmonary involvement tends to be mild, but diffuse lung involvement becomes apparent if treatment is not given promptly. Generalized lymphadenopathy and hepatosplenomegaly develop in 50% of cases, and meningitis develops in 20% to 40%. The most common signs of miliary TB include malaise, anorexia, weight loss, and fever ranging from low to high grade. The CXR shows a particular nodular pattern with multiple very small opacities scattered bilaterally (called miliary due to the resemblance to millet seeds).

DIAGNOSIS

In general, TB in a child can be discovered in 3 ways: through contact investigation of an active contagious TB case, through screening of children with other high epidemiological risks, and through evaluation of children presenting with symptoms and signs suspicious for TB.⁶ The first 2 ways allow for an early diagnosis, when children are asymptomatic or mildly symptomatic. Children identified in a contact investigation, with other epidemiological risks or with suspicious symptoms, should be tested for TB infection, using one of 2 different methods currently available: tuberculin skin test (TST) or interferon- γ release assays (IGRAs). Both methods are indirect because they test the individual's adaptive immune response to MTB.

Neither of them excludes TBI nor distinguishes TBI from TB disease. However, a positive IGRA correlates with progression to disease more strongly than a positive TST.¹¹

Tuberculin Skin Test or Mantoux Skin Test

It involves intradermal injection of 0.1 mL of purified protein derivative containing 5 tuberculin units. The results are interpreted as the transverse diameter of induration present 48 to 72 hours after injection. This test has been used for decades. However, it has many disadvantages, including a low specificity. Factors such as very young age, malnutrition, immunosuppression by disease or drugs, viral infection, recent measles vaccination, and overwhelming TB can result in a false negative. False-positive results can be caused by cross-sensitization to antigens of nontuberculous mycobacteria and previous immunization with Bacille Calmette-Guérin (BCG) vaccine. To try to improve the specificity, there are 3 reaction size limits for determining a positive result based on epidemiological and clinical risk factors (Table 1). To interpret the results correctly, it is important to obtain an adequate history of possible risk factors for acquiring TBI.⁶ Other disadvantages include the need for a second visit to read the results, a lack of adequate training and experience in administration, a wide range of inter-reader variability, and boosting phenomenon (ie, a reaction to TST occurring in a person previously infected with TB or in children vaccinated with BCG whose immune response has waned over time and the tuberculin test stimulates or "boosts" their immune system; the reaction does not represent a new infection but a boosted immune response).

Interferon- γ Release Assays

These tests measure in vitro interferon gamma (IFN- γ) production from peripheral blood T-lymphocytes after stimulation with 2 purified antigens derived from the MTB complex. Two IGRAs are approved and commercially available in the

TABLE 1. Size of Induration That Defines a Positive Tuberculin Skin Test According to Risk Factors

Induration Size	Risk Factors
≥5 mm	• Close contacts of known or suspected contagious cases • Suspected TB disease (abnormal chest radiograph or clinical evidence) • HIV infection, other immunosuppressive conditions (eg, s/p organ transplant), or receiving immunosuppressive therapy (eg, high-dose prolonged course of corticosteroids or TNF-α antagonists)
≥10 mm	• Birth in a high-prevalence country • Previous residence or significant travel to a high-prevalence country • Certain medical risk factors: diabetes mellitus, silicosis, chronic renal failure, malnutrition, Hodgkin disease, lymphoma • High-risk populations (persons experiencing homelessness, injecting or using illegal drugs, or living in high-risk congregate settings, such as nursing homes, homeless shelters, or correctional facilities) • Children with frequent exposure to adults living with HIV and other high-risk adults as above • Age younger than 4 years
≥15 mm	• No risk factors

Abbreviations: s/p, status post; TB, tuberculosis; TNF- α : tumor necrosis factor-alpha.

United States: QuantiFERON-TB Gold Plus (QFT; Qiagen) and T-SPOT.TB test (T-Spot; Oxford Immunotec).

These tests have higher specificity than the TST due to the use of more specific MTB antigens, which are not found in BCG vaccine or in most common nontuberculous mycobacteria, such as *Mycobacterium avium* complex. However, these antigens are found in other much less common species such as *M kansasii*, *M marinum*, *M szulgai*, and *M flavescens*.

Both IGRAs contain negative and positive controls in addition to the MTB-specific antigens to aid in test interpretation. Too much IFN- γ response to the negative control or too little response to the positive control yields indeterminate (QFT) or invalid (T-Spot) results. These results cannot be interpreted and should not be used in clinical decision-making. Factors associated with indeterminate or invalid results include young age, immunocompromised status, and inappropriate handling of the sample. The results of the T-Spot test seem to be less affected by these factors.

The sensitivity of IGRAs is relatively similar to that of TST, ranging from 80% to 90% in patients with culture-proven TB disease. The pool specificity of IGRAs ranges from 92% to 97%, which is significantly higher than that of TST (as low as 60% in populations with high BCG vaccination rates).¹² False-positive and false-negative results may occur due to errors in collection, processing technique, and storage. Infections with certain species of nontuberculous

TABLE 2. Comparison of IGRA and TST

IGRA	TST
In vitro test	In vivo test
Two specific antigens	Multiple antigens; many are not specific for MTB
No boosting	Boosting phenomenon
One patient visit	Two patient visits
Minimal inter-reader variability	Significant inter-reader variability
Results in 24 hours (when done in-house)	Results in 48 to 72 hours
Requires phlebotomy	No phlebotomy, but correct administration requires training
Higher specificity	Lower specificity
Not affected by BCG or most nontuberculous mycobacteria	Cross-reacts with BCG and nontuberculous mycobacteria

Abbreviations: BCG, Bacille Calmette-Guérin; MTB, *Mycobacterium tuberculosis*.

mycobacteria, such as *M kansasii*, *M marinum*, and *M szulgai*, can also cause a false-positive result. Low-grade positive IGRA results may be false positive. In low-risk situations with a low-grade positive IGRA, the other IGRA or TST should be done and only be accepted as truly positive if 2 tests are positive.^{7,13} IGRAs have many advantages over TST. A summarized comparison of IGRAs and TST is presented in Table 2.

Historically, there has been hesitation to use IGRAs in very young children (aged younger than 2 years) due to the scarcity of data on this population when these tests were originally Food and Drug Administration (FDA) approved. The main concern has been the perception of lower sensitivity of IGRAs compared with TST in these children, who, on the other hand, are at very high risk for developing severe TB disease if they get infected. In a study by the Centers for Disease Control and Prevention (CDC) comparing TST vs IGRAs in asymptomatic foreign-born children living in the United States, the positive predictive value was 10% for TST compared with 73% to 79% for IGRAs in children younger than 5 years, and 60% for TST vs 98% to 99% for IGRA in children aged 5 years and older.¹⁴ In practical terms, if the TST is positive but the IGRA is negative in asymptomatic BCG-vaccinated children without a history of exposure to an adult/adolescent TB case, TBI is unlikely. Data supporting the use of IGRAs in children of all ages have continued to increase, and many pediatric TB experts have used IGRAs regularly in children of all ages for a few years (personal communication). In 2023, a review of published studies on the use of IGRAs in children that included data on children younger than 2 years found that after a follow-up period of 3 to 5.7 years, progression to TB disease did not occur in

any of 575 untreated children with negative IGRAs, including 70 children with positive TST.¹¹

In 2024, the American Academy of Pediatrics (AAP) changed their recommendation from limiting the use of IGRAs to children aged older than 2 years to using these tests in children of any age.⁷ In fact, IGRAs are preferred in most cases, but particularly in children vaccinated with BCG. Other factors to consider when deciding to use IGRAs in young children are the availability of a phlebotomist trained in venipuncture in infants, reluctance of parents, and availability of courier services to transport the samples in a timely fashion.

Routine testing with both IGRA and TST is not recommended. However, results from both tests may be helpful in certain clinical scenarios, such as when the initial test is negative in a child with clinically suspected TB, or in an immunocompromised child with epidemiological risk factors for TB. In these cases, a positive result from either test should be interpreted as reflective of TB infection. *Of note, a negative result for either an IGRA or a TST should be considered unreliable in infants aged younger than 3 months.*⁷

Once a child tests positive for TST or IGRA, the next step is to assess whether the child has TB disease or TBI. A detailed history of symptoms and exposures is of utmost importance, followed by a thorough physical examination. Chest x-rays (both posterior-anterior and lateral views) should be performed in every child that tests positive for TBI. Because the radiographic findings in primary pulmonary TB can be very subtle, it is recommended that CXRs be reviewed by an expert in pediatric TB, whenever possible. It is strongly recommended that a lumbar puncture be performed to rule out meningitis in all children younger than 1 year with suspected TB disease even if they have no central nervous system (CNS) signs or symptoms, as well as in any child with CNS signs/symptoms. Other evaluations will depend on the clinical presentation.

The next diagnostic step, once TB disease is suspected, is to obtain appropriate samples to send for mycobacterial stain, cultures, and molecular tests. It is important to emphasize that often culture confirmation in children with TB may not be necessary. If a child is a known contact with an infectious case of TB, has a positive test of infection, and has clinical or radiographic findings suggestive of TB, that child should be treated for TB disease. The drug susceptibility testing results of a source case's isolate can be used to determine the best treatment regimen. However, obtaining cultures is recommended when the source case is unknown, when there is known or suspected drug-resistant MTB, when the child is immunocompromised, and in cases of extrapulmonary TB (when obtaining samples is easier).

Acid-Fast Bacilli Stain and Mycobacterial Cultures

Samples appropriate for cultures include gastric aspirates, induced sputum, spontaneous sputum, cerebrospinal fluid (CSF), urine, and other fluids or tissue obtained according to the patient's age and clinical presentation. Gastric aspirates should be obtained in the early morning before the child gets up and peristalsis empties the stomach of the secretions swallowed overnight. For gastric aspirates and sputum cultures, it is recommended to send 3 samples obtained daily for 3 days. The yield of acid-fast bacilli (AFB) stain in gastric aspirates is extremely low (less than 10%). The yield of culture of 3 gastric aspirates is less than 50% in children and less than 75% in infants. Sputum samples obtained after induction with hypertonic saline have been reported as having a better yield and are relatively easily done in children older than 5 to 7 years.¹⁵ In some studies, nasopharyngeal aspiration after induced cough was successful and safe in infants.¹⁶ Samples obtained via bronchoscopy do not necessarily have a better yield than those obtained via gastric aspirates.¹⁷

Molecular Tests: Nucleic Acid Amplification Tests and Polymerase Chain Reaction

Tests using polymerase chain reaction (PCR) offer rapid confirmation of the presence of MTB in clinical samples. The sensitivity of traditional PCR has varied from 25% to 83% when compared with clinical diagnosis in children.⁶ A negative PCR result does not rule out TB in a child. GeneXpert MTB/RIF (Xpert; Cepheid) is the most readily available automated PCR-based test. It can be done in a wide variety of samples, including sputum, gastric aspirates, nasopharyngeal aspiration, and stools, although it is only FDA approved in sputum. In a systematic review of pediatric studies, using positive culture as the gold standard, Xpert's pooled sensitivity was 65% in sputum samples, 73% in gastric aspirates, 62% in stools, and 46% in nasopharyngeal aspirates. The pooled specificity was similarly high in all specimens (>98%). Additionally, Xpert showed high sensitivity and specificity for the detection of rifampin resistance (90% and 99.8%), which makes it particularly helpful when drug-resistant TB is suspected. The Xpert MTB/RIF Ultra (Ultra; Cepheid) is a second-generation test with reported improved sensitivity, especially in patients with paucibacillary disease (pulmonary TB with negative AFB smear results and positive *M tuberculosis* culture results from respiratory specimens) such as children and patients with HIV. Ultra is not FDA approved and is not available in the United States.¹⁸ The World Health Organization (WHO) recommends the use of Xpert in children as an initial test in sputum, gastric aspirate, nasopharyngeal aspirate, and stool

rather than smear microscopy/culture, and the use of Ultra in sputum or nasopharyngeal aspirates. The WHO also supports the use of Xpert in other fluids and tissue (eg, CSF and lymph node).^{19,20} Because of its decreased sensitivity compared with cultures and because an isolate is required to perform a complete drug susceptibility testing, Xpert should not replace mycobacterial cultures in the United States. However, the combination of the 2 methods is helpful in the management of TB.

MANAGEMENT

Management of Exposure

The management of exposed children varies depending on the risk for acquiring the infection and the risk for developing TB disease once infected. After a child with risk factors for TB infection is identified, the next factor to consider is the risk of developing TB disease, which is directly related to the status of their immune system. Children younger than 5 years are at high risk due to the immaturity of their immune system. Primary or acquired immunodeficiency syndromes and certain immunosuppressive therapies also put patients at high risk for TB disease.

Children younger than 5 years who are exposed to TB should be fully evaluated with a comprehensive review of systems and physical examination, a test for infection (TST or IGRA), and a CXR. If all evaluation is normal and/or negative, these children should be placed on primary prophylaxis (also known as “window prophylaxis”) with isoniazid (INH) or rifampin (RIF). A repeat test of infection is done 8 to 10 weeks after their last exposure.⁷ If the repeat test is also negative, the prophylaxis should be discontinued. If it is positive, these children should complete a course for TBI.

For immunocompromised children, window prophylaxis and retest are also recommended. In most cases, if the repeat IGRA or TST is negative, prophylaxis is discontinued. However, the sensitivity of the test may be too low to rule out infection when the degree of immunosuppression is high. In this case, TBI cannot be excluded, and treatment course should be completed.

For all other patients, the evaluation should include IGRA or TST, followed by a CXR if IGRA or TST is positive or if there are symptoms suggestive of TB. Window prophylaxis is not indicated, but repeat IGRA or TST testing 8 to 10 weeks after exposure is recommended. If the second test is negative, no further evaluation or treatment is necessary.

Treatment of TB

The drugs used for the treatment of TB depend on the pattern of resistance of the presumptive or proven MTB isolate. These patterns are classified as follows:

Drug-susceptible MTB (DS-TB): isolate is susceptible to all first-line anti-TB drugs.

Drug-resistant MTB (DR-TB): isolate is resistant to at least one of the first-line drugs.

Multidrug-resistant MTB (MDR-TB): isolate is resistant to isoniazid and rifampin.

Extensively drug-resistant MTB (XDR-TB): isolate is resistant to isoniazid, rifampin, any fluoroquinolone, and either bedaquiline or linezolid (or both).

Pre-extensively drug-resistant MTB (Pre-XDR-TB): isolate is resistant to isoniazid, rifampin, and a fluoroquinolone or a second-line injectable drug (eg, amikacin, capreomycin, and kanamycin).

Treatment of TBI

Traditionally, a regimen of daily INH for 6 to 9 months was considered the gold standard treatment for DS-TB infection for many years. The 9-month regimen is almost 98% effective in preventing TB disease. However, anecdotal experience and epidemiologic studies have demonstrated that adherence and completion rates are low. Shorter courses using rifamycins alone or in combination with INH are as effective with much better adherence and completion rates. These regimens (summarized in Table 3) are now preferred over the longer regimens.²¹

For presumptive MDR-TB infection, levofloxacin (LFX) or moxifloxacin (MFX) with or without a second drug daily for 6 to 12 months is recommended. Possible second drugs include ethambutol (EMB) or ethionamide (ETA). The combination of fluoroquinolones and pyrazinamide (PZA) has a higher risk of poor tolerance and/or toxicity and is not recommended. A recent study demonstrated 56% efficacy of 6 months of LFX alone compared with placebo in children and adolescents exposed to MDR-TB.²² Six months may be appropriate for some patients. However, an extended duration (ie, 9 or 12 months) is recommended by many TB experts for patients with immunosuppression, children younger than 5 years, and individuals with other substantial risk for progression to active TB disease. For pre-XDR-TB or XDR-TB, consultation with a pediatric TB expert is recommended.

Treatment of TB Disease

Drug-susceptible TB

Six-month regimen (2HRZE/4HR)

This regimen consists of an intensive phase of 2 months with INH (H), RIF (R), PZA (Z), and EMB (E), also known as RIPE, followed by a continuation phase of 4 months of INH/RIF to complete a total treatment time of 6 months. Medications are usually given every day for the first 2 weeks to 2 months of therapy. After this time, medications can be

TABLE 3. Recommended Regimens for the Treatment of Drug-Susceptible TB Infection in Children and Adolescents

Abbreviated Name	Drugs	Frequency	Duration	Comments
Preferred regimens				
3HP ^a	Isoniazid plus rifapentine	Once weekly	3 months (12 weeks)	Preferred regimen for children aged 2 years and older Drug interactions, high pill burden, cost
4R	Rifampin	Daily	4 months (120 doses)	Preferred regimen for children younger than 2 years Choice for INH-resistant TB Drug interactions
3HR	Isoniazid-rifampin	Daily	3 months	Consider when 3HP and 4R are not available Drug interactions
Alternative regimens				
9H or 6H ^b	Isoniazid	Daily or twice weekly under DOT	9 months (6 months) ^b	Long duration, poor adherence, low completion rates

Abbreviations: DOT, directly observed therapy; INH, isoniazid; TB, tuberculosis.

^aNot approved for children younger than 2 years.

^bIn the United States, INH for 9 months is preferred over 6 months, but 6 months is acceptable. The World Health Organization recommends INH for 6 months.

given safely and effectively twice or thrice weekly under directly observed therapy (DOT). For children without extensive disease and no risks for drug-resistant TB, many experts treat using only 3 drugs (INH, RIF, and PZA) for the initial intensive phase and INH/RIF for the other 4 months. For patients with cavitary pulmonary disease and/or patients with persistent positive sputum cultures after 2 months, the continuation phase is extended for another 3 months, for a total of 9 months. This regimen is used for pulmonary and most extrapulmonary TB, except for meningitis and osteoarticular disease, for which the duration may be extended to up to 12 months. For meningitis, the AAP recommends one of the following drugs as the fourth drug instead of EMB: ETA or LFX or MFX for the intensive phase.⁶ However, the WHO has endorsed a 6-month intensive regimen with the 4 drugs (6HRZE) as an alternative to the 12-month regimen.¹⁹ The use of corticosteroids has been shown to improve outcomes in TB meningitis, and prescribing corticosteroids is strongly recommended.

Four-month regimen (2HRZE/2HR)

This regimen was endorsed by the WHO and CDC after an international multicenter randomized trial demonstrated its noninferiority as compared with the 6-month regimen.¹⁹ It has been endorsed by AAP in 2024.⁷ It is acceptable for children between the ages of 3 months and 16 years with negative AFB smear, nonsevere TB disease, defined as peripheral lymph node TB; intrathoracic lymph node TB without significant airway obstruction; uncomplicated TB pleural effusion or paucibacillary, noncavitary parenchymal disease, confined to less than one lobe of the lungs (ie, extensive pneumonia

involving the whole lobe would be disqualifying), and without a miliary pattern. This regimen consists of 2 months of HRZE plus 2 months of INH/RIF for a total duration of 4 months. As with the longer regimen, EMB in the first 2 months of treatment is recommended in settings with a high prevalence of HIV or of INH resistance. Otherwise, that initial phase can be done with only 3 drugs.

Four-month rifapentine-moxifloxacin-based regimen (HPMZ)

After a randomized study showed noninferiority of this regimen compared with the 6HRZE/4HR, HPMZ was endorsed by the CDC in February 2022²³ and the AAP in 2024.⁷ It is an acceptable regimen for children aged 12 years and older and with body weight greater than or equal to 40 kg with pulmonary TB.²⁴

Some experts also use it in other paucibacillary disease, such as peripheral lymphadenopathy or uncomplicated pleural TB. It consists of 8 weeks of INH, rifapentine (P), MFX, and PZA given daily, followed by a 9-week continuation phase of the same drugs without PZA given daily for a total duration of 17 weeks.

Drug-resistant TB

A detailed discussion of DR-TB is beyond the scope of this article. Consultation with a pediatric TB expert is recommended when DR-TB is confirmed or suspected.

Historically, regimens for MDR-TB used a combination of oral and injectable drugs for 18 to 24 months. The WHO divided drugs used in these regimens into 3 groups (A, B, and C, based on their efficacy, safety profile, and experience of use; Table 4). Thanks to the development of new drugs (eg, bedaquiline/BDQ, delamanid/DLM, and

TABLE 4. World Health Organization's Drug Groups for Treatment of MDR-TB

Group	Drugs (Abbreviation)	Steps for Creating an MDR-TB Treatment Regimen When Shorter Courses Cannot Be Used
A	Levofloxacin (LFX) or moxifloxacin (MFX) Bedaquiline (BDQ) Linezolid (LZD)	Choose one fluoroquinolone and both BDQ and LZD
B	Clofazimine (CFZ) Cycloserine (CS)	Add at least one drug. Use both drugs, if possible
C	Ethambutol (EMB) Delamanid ^a (DLM) Pyrazinamide (PZA) Imipenem-cilastatin or Meropenem (MPM) Ethionamide (ETA) Paraaminosalicylate (PAS) Amikacin or Streptomycin	Add additional drugs from this group according to drug susceptibility testing results for the desired number of drugs in the regimen The use of DLM should be prioritized

Abbreviation: MDR-TB, multidrug-resistant tuberculosis. Pretomanid is not included in this table because it is only used in combination with bedaquiline, linezolid $\pm$ moxifloxacin (BPAL/BPaLM regimen).

^aDLM is available only through compassionate use program in the United States.

pretomanid/Pa) and repurposing of other drugs (eg, LFX, MFX, and linezolid/LZD), new shortened regimens for MDR-TB using all oral medications from 6 months to 12 months have been developed, tested, and approved.^{25,26}

Six-month all oral regimen (BPAL/BPaLM)

This regimen consists of BDQ, Pa, and LZD $\pm$ MFX taken orally daily for 6 months. The course could be extended to 9 months when there is delayed treatment response within the first 8 weeks. BPAL/BPaLM is WHO approved in persons aged 14 years and older without previous exposure to the 3 key drugs (>1 month). However, because pretomanid is not FDA approved in children, this regimen is not approved for children younger than 18 years in the United States.^{24–29}

WHO standardized all-oral short regimen

This regimen consists of all drugs in WHO groups A and B plus 1 drug from group C, prioritizing the use of DLM. However, DLM is available only through compassionate use program in the United States. The duration is 9 to 12 months. This regimen can be used in children of all ages with MDR-TB without extensive or severe extrapulmonary disease.^{19,20}

The Sentinel Project Pediatric Drug-Resistant Tuberculosis shortened regimen is very similar to the WHO shortened regimen.³⁰ Additionally, the following recommendations for duration of therapy are included: 6 to 9 months for nonsevere TB, 9 to 12 months for severe disease, and at least 12 months for osteoarticular disease.

Courses of longer duration

Shortened courses are not appropriate for treatment of extensive TB disease with or without involvement of sites with poor drug penetration (eg, disseminated or miliary, meningitis, and osteoarticular TB), when there is suspected or

proven extensive drug resistance (pre-XDR or XDR-TB), or when the child is immunocompromised. The treatment regimen should be modified/extended when the child cannot take or tolerate one or more of the core drugs, when there is a slow clinical response, and when there are many treatment interruptions due to adverse effects or tolerance.^{19,20}

Monitoring During Treatment

Monitoring is essential for the success of a treatment regimen. The role of the public health department is key for assuring adherence via DOT, offering psychosocial support, and monitoring for drug-related adverse effects. Routine laboratory monitoring of liver function during treatment of TBI and most cases of TB disease is not recommended because hepatitis is a rare adverse effect in previously healthy children. However, these tests should be performed in children with clinical signs and symptoms of hepatitis (eg, jaundice, nausea, vomiting, and abdominal pain), children with preexisting liver disease, or children taking other hepatotoxic drugs. When using second-line anti-TB drugs, other monitoring tests specific to each drug might be indicated. Therapeutic drug monitoring is an important tool for situations where drug-drug interactions or malabsorption may affect drug levels. It is especially useful when using drugs that may not be well studied in children, such as second-line drugs or drugs used to treat MDR-TB, or when there is a poor clinical response to what would be considered an appropriate regimen.³¹

PROGNOSIS

With early detection and appropriate treatment, the prognosis of TB disease in children is excellent. This is particularly true in cases of DS-TB, with success rates above 90%. Lower success rates are seen in children with extreme malnutrition

and HIV coinfection.³² Delays in making the diagnosis and initiating treatment correlate with unfavorable outcomes, especially in meningitis and disseminated disease. In cases of MDR-TB in children, the reported rates of success have been close to 80%. In a retrospective cohort study among children treated for MDR-TB, the use of one or more of the new or repurposed drugs (ie, BDQ, DLM, and LZD) in the treatment regimen was associated with a higher proportion of favorable outcomes compared with regimens without any of those drugs (94% vs 80%).³³

Summary

- Testing for tuberculosis infection (TBI) should only be performed in children with risk factors for TB, recognizing that the most important risk factor is being a household contact of an active TB case.^{6,7} (Based on research evidence and consensus)
- Interferon- γ release assays (IGRAs) are equally acceptable testing methods as the tuberculin skin test (TST) to diagnose TBI in children of all ages.^{7,11,14} (Based on moderate research evidence [cumulative cohort data] and consensus)
- IGRAs have many advantages over TST and in many situations is a better test, especially in Bacille Calmette-Guérin (BCG)-vaccinated children.^{7,13} (Based on research evidence and consensus)

- Nucleic acid amplification tests (NAATs), including GeneXpert MTB/RIF (Xpert), are useful tools for rapid detection and confirmation of *Mycobacterium tuberculosis* (MTB) in various clinical samples.¹⁹ However, NAATs should be used in conjunction with mycobacterial cultures.⁷ (Based on research evidence and consensus)
- A short (3- to 4-month) treatment regimen for TBI is preferred over longer (6- to 9-month) regimens because of better adherence and completion rates with similar efficacy.^{7,21} (Based on strong research evidence and consensus)
- Children older than 3 months with nonsevere TB disease and without suspicion for multidrug-resistant TB (MDR-TB) can be treated with a shortened (4-month) regimen using 3 to 4 drugs.^{7,19} (Based on strong research evidence and consensus)
- Children without extensive or severe MDR-TB disease can be treated with a combination of all oral drugs instead of using injectable drugs and for 9 to 12 months instead of 18 to 24 months.^{19,30} (Based on strong research 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 March 1, 2025).



1. A 4-year-old girl with pauciarticular juvenile idiopathic arthritis and uveitis has been unresponsive to prior treatment with corticosteroid and methotrexate. Her pediatric rheumatologist has discussed with the family starting a tumor necrosis factor (TNF) inhibitor (adalimumab). An IGRA (QuantiFERON-TB Gold test) is performed and results as low-grade positive. She has no known tuberculosis (TB) exposure and has not traveled outside the United States. She does not have respiratory symptoms or fever. She is well appearing, and her lungs are clear to auscultation. Which of the following is the most appropriate next step in management?
 - A. Begin isoniazid (INH)
 - B. Begin INH and rifampin
 - C. Begin rifampin
 - D. Perform T-SPOT IGRA
 - E. Repeat the QuantiFERON-TB Gold test in 2 weeks
2. A healthy 14-year-old girl is applying for a volunteer position at the hospital. She was born in India and received BCG immunization as a newborn. The family immigrated to the United States when she was aged 2 years. She traveled to India 7 years ago for 2 weeks, but otherwise, she has not traveled internationally since. There is no known contact with anyone with TB. A tuberculin skin test (TST) was required to volunteer at the hospital and resulted with 10 mm induration. A chest x-ray was normal. An IGRA is performed and is negative. She is asymptomatic with a normal physical examination. Which of the following is the most appropriate next step in management?
 - A. Begin INH
 - B. Begin INH plus rifapentine
 - C. No further management is indicated
 - D. Repeat the IGRA in 6 weeks
 - E. Repeat the TST in 6 weeks
3. A 7-month-old boy was admitted to the hospital 5 days ago for pneumonia. He presented with intermittent fevers for 8 days with cough, wheezing, malaise, and decreased feeding. He is fully immunized. A chest x-ray showed a right middle lobe infiltrate with hilar adenopathy. He has not improved on intravenous (IV) ampicillin or on IV ceftriaxone. His history is negative for seizures and there are no focal neurologic deficits on examination. The infant and parents returned from a 2-week stay with family in Brazil 4 weeks ago. An IGRA assay on the patient is strongly positive. In addition to obtaining gastric aspirates and initiating antituberculosis therapy, which of the following is the most appropriate next step in management?
 - A. Brainstem auditory evoked response
 - B. Bone scan
 - C. Computed tomographic scan of the head
 - D. Lumbar puncture
 - E. Ophthalmology consultation

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4. A 20-month-old boy was exposed to his visiting grandmother for a 1-week timeframe 2 to 3 weeks ago. The grandmother was noted to be coughing, and she has now been diagnosed with drug-susceptible pulmonary TB. The infant is asymptomatic with a normal physical examination and a normal chest x-ray. IGRA on the infant is negative. Which of the following is the most appropriate next step in management?
- A. Apply TST today and if negative repeat in 2 to 4 weeks
 - B. Begin INH and repeat IGRA assay in 8 to 10 weeks
 - C. Begin INH for 9 months with no further testing
 - D. Begin rifampin, INH, and pyrazinamide and repeat IGRA assay in 4 to 6 weeks
 - E. Repeat IGRA assay in 8 to 10 weeks and no antituberculosis drug therapy
5. A 3-year-old girl is brought to the emergency department by her parents with a 15-day history of intermittent fever and occasional cough. Today she is not moving her left arm and leg. The family immigrated to the United States 5 weeks ago from Indonesia. Her mother states that yesterday she learned that a family friend in Indonesia who often had contact with the patient was diagnosed with TB 3 weeks ago. A chest x-ray on the 3-year-old girl is suspicious for pulmonary TB. Brain magnetic resonance imaging shows T2-weighted signal hyperintensity in the subcortical and deep white matter regions. There are areas of restricted diffusion in the right basal ganglia. A lumbar puncture is done, and cerebrospinal fluid (CSF) shows low glucose, elevated protein, and pleocytosis. CSF polymerase chain reaction is positive for *Mycobacterium tuberculosis* and negative for rifampin resistance. Which of the following is the most appropriate initial pharmacotherapy?
- A. INH, rifampin, and ethambutol
 - B. INH, rifampin, ethambutol, and linezolid
 - C. INH, rifampin, and pyrazinamide
 - D. INH, rifampin, pyrazinamide, levofloxacin, and corticosteroid
 - E. Rifampin, pyrazinamide, ethambutol, and linezolid



A High-Pressure Case of Constipation and Seizures

Taylor J. Kulik, MD,¹ Zachary J. Pettigrew, MD^{1,2}

¹University of North Carolina, Chapel Hill, North Carolina

²Moses H. Cone Memorial Hospital, Greensboro, North Carolina

PRESENTATION

An 8-year-old previously healthy boy presents to a community emergency department (ED) for constipation and altered mentation. Over the past several weeks, he has developed mild intermittent abdominal pain that occurs several times daily. The patient is unable to describe the pain, but his parents deny any inciting or alleviating factors. He has had associated decreased appetite, abdominal distension, and strained stooling, with his stool itself becoming progressively loose. Parents report large-volume diarrhea beginning the day prior to presentation, at which time they noticed a “bulge” in his perianal area. There has been no gross blood in his stool or at his rectal orifice. For the past day he has been acting differently, with episodic slurred speech and disorientation that spontaneously resolve. Parents deny recent emesis, headache, weight loss, fever, or apparent discrete illness. He has no history of constipation or laxative use. Further history reveals several weeks of paroxysmal bilateral lower extremity pain noted to occur every few days, without clear precipitating factors, diurnal variation, nighttime awakening, or functional impairment. He has been evaluated multiple times by his pediatrician for his leg pain. Physical examination, vital signs, complete blood count, and plain film results of his legs were normal, and parents were counseled that his symptoms likely represented growing pains. Although not previously affecting his gait, the pain has increased in frequency and is now accompanied by 3 weeks of subjective weakness with occasional hunched posture while walking. He has attention deficit hyperactivity disorder (ADHD) managed with methylphenidate at a stable dose. A few days prior to this presentation to the ED, he was started on clonidine to assist with chronically poor sleep. He has normal neurodevelopment and has appropriately progressed through school. His behavior, school attendance, and academic performance have not changed over the past several months. He has not received any recent immunizations and is up to date on age-appropriate vaccines.

While in the ED, he has 2 generalized tonic-clonic seizures, the first while straining to defecate. He received parenteral benzodiazepines for both seizures and did not return to baseline between events. Initial vital signs shortly after his first seizure reveal blood pressure of 155/112 mm Hg with heart rate 120 beats per minute (bpm), temperature 36.9 °C (98.5 °F), and respiratory rate 21 breaths per minute with 96% oxygen saturation on room air. His blood pressure remains serially elevated in the ED (maximum 177/116 mm Hg). Physical examination after the second seizure reveals mild rectal prolapse without focal abdominal or neurologic findings. He is noted to be sleepy but appropriately oriented. Selected results from initial laboratory evaluation are summarized in Table 1. Radiographs are ordered to evaluate

AUTHOR DISCLOSURE: Dr Kulik is now at the University of Kentucky, Kentucky Children’s Hospital. Drs Kulik and Pettigrew 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. This case is based on a poster presented by Drs Kulik and Pettigrew at the Pediatric Hospital Medicine Conference, Lake Buena Vista, FL, on July 29, 2022 as part of the Clinical Conundrums session.

ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ARMS	alveolar RMS beats per minute
CT	computed tomography
ED	emergency department
EFS	event-free survival
ERMS	embryonal RMS
GN	glomerulonephritis
ICP	intracranial pressure
IV	intravenous
MRI	magnetic resonance imaging
PICU	pediatric intensive care unit
PRES	posterior reversible encephalopathy syndrome
RMS	rhabdomyosarcoma

TABLE 1. Summary of Selected Initial Laboratory Results

Laboratory Index	Value ^a	Reference Range
Chemistry		
Serum sodium	136 mEq/L (136 mmol/L)	135–145 mEq/L (135–145 mmol/L)
Serum potassium	3.4 mEq/L (3.4 mmol/L)	3.5–5.0 mEq/L (3.5–5.0 mmol/L)
Serum calcium	9.9 mg/dL (2.5 mmol/L)	8.5–10.5 mg/dL (2.1–2.6 mmol/L)
Serum bicarbonate	18 mEq/L (18 mmol/L)	22–32 mEq/L (22–32 mmol/L)
Serum glucose	118 mg/dL (6.6 mmol/L)	80–110 mg/dL (4.4–6.1 mmol/L)
Blood urea nitrogen	18 mg/dL (6.4 mmol/L)	5–18 mg/dL (1.8–6.4 mmol/L)
Serum creatinine	0.76 mg/dL (58 μmol/L)	0.30–0.70 mg/dL (23–53 μmol/L)
Aspartate aminotransferase	63 U/L (1.1 μkat/L)	15–40 U/L (0.2–0.7 μkat/L)
Alanine aminotransferase	25 U/L (0.4 μkat/L)	15–40 U/L (0.2–0.7 μkat/L)
Total serum bilirubin	0.5 mg/dL (8.5 μmol/L)	0.2–1.0 mg/dL (3.4–17 μmol/L)
Blood count		
Leukocyte count	19 500/μL (19.5 × 10⁹/L)	4500–13 500/μL (4.5–13.5 × 10 ⁹ /L)
Absolute neutrophil count	16 300/μL (16.3 × 10⁹/L)	1500–8000/μL (1.5–8.0 × 10 ⁹ /L)
Hemoglobin	11.9 g/dL (119 g/L)	11.0–14.6 g/dL (110–146 g/L)
Platelet count	449 × 10³/μL (449 × 10⁹/L)	150–400 × 10 ³ /μL (150–400 × 10 ⁹ /L)

^aValues outside of the corresponding laboratory reference range are denoted in bold font.

his abdominal distension. Abdominal x-ray shows a moderate proximal colonic stool burden with complete opacification of the recto-sigmoid colon and a nonobstructive bowel gas pattern (Figure 1). On chest x-ray, there are incidentally noted rounded opacities in both lungs, interpreted as possible pulmonary interstitial thickening (Figure 2).

The inpatient pediatrics team at the nearest children's hospital is contacted for admission. Concerns regarding the patient's hypertension, seizures, and rapid-onset stooling difficulties are jointly acknowledged by the referring and accepting teams. However, after collaborative discussion, expedited transfer to the pediatrics unit is deemed prudent



FIGURE 1. Anterior-posterior abdominal x-ray showing moderate colonic stool burden, primarily involving the ascending and proximal transverse colon. The descending colon appears empty. There is a nonobstructive bowel gas pattern. The recto-sigmoid colon is completely opacified. No intraperitoneal free air or portal venous gas is present.



FIGURE 2. Anterior-posterior abdominal x-ray incidentally demonstrating rounded opacities projecting over the bilateral lungs, denoted by arrows. The span of the largest lesion (labeled "1"), present in the right lower lung field, is marked and measures 3.4 cm. The quality of the study is limited by extensive overlying wires and leads.

to prioritize patient safety, stabilization, and continuation of necessary evaluation. It is not known whether neuroimaging, abdominal ultrasound, or advanced abdominal imaging were considered or available at the referring facility.

Upon arrival to the inpatient unit, he remains tired but appropriately oriented and interactive. Admission manual blood pressure is 166/112 mm Hg with heart rate 90 bpm; other vitals are within normal limits. He weighs 23 kg (15th percentile for age and sex) and is 1.26 m tall (23rd percentile) with a corresponding body mass index of 14.6 (16th percentile). He appears well-nourished with a thin body habitus and normal craniofacial features. Pupils are symmetrically dilated and readily reactive to light. Extraocular movements and cranial nerves II to XII are intact. Head is atraumatic, oropharynx is clear, and neck is supple with full range of motion and no lymphadenopathy. Cardiac auscultation shows normal rate and regular rhythm without murmurs. Lungs are clear and well-aerated bilaterally without adventitious sounds. Abdomen is soft, nondistended, and nontender without appreciable mass or hepatosplenomegaly. His bladder is distended with the superior dome palpable several centimeters inferior to the umbilicus; parents note that he has not voided in 10 hours. Rectum is mildly prolapsed. Extremities are normal without injury, deformity, swelling, or ecchymosis. No rashes or dermatologic lesions are visible. There are no gross focal motor deficits. He can ambulate with assistance. Gait is slow but coordinated. Further neurologic examination, including fundoscopy and testing for strength, sensation, and reflexes, cannot be adequately performed due to rapidly escalating bilateral thigh pain. Several minutes later, he has a 2-minute generalized tonic seizure that readily aborts with intravenous (IV) lorazepam. Antihypertensive therapy is indicated given the severity of hypertension and neurologic sequelae; he receives emergent intervention with IV hydralazine. He is taken for an emergent noncontrast head computed tomography (CT), which is normal without evidence of intracranial space-occupying mass, hemorrhage, hydrocephalus, or edema. Upon return from the radiology suite, he is transferred to the pediatric intensive care unit (PICU) for closer neurologic and hemodynamic surveillance, where he is started on an antihypertensive infusion.

DISCUSSION

Differential Diagnosis

Our patient's array of clinical features necessitated an organized, problem-based approach to his differential diagnosis. The 2 most immediate problems to address, and thus the focus of our approach, were his new-onset generalized

seizures and severe hypertension. His subtle mental status changes altered stool patterns, paroxysmal leg pain, and incidentally discovered pulmonary radiographic abnormalities were also considered as contributory. Although his more indolent symptoms could have been unrelated to his acute deterioration, attempts to find a unifying diagnosis for his entire presentation guided our diagnostic approach.

The initial evaluation of his seizures favored secondary causes of seizures as opposed to a primary seizure disorder, given his associated clinical findings. Our most immediate etiologic concern was increased intracranial pressure (ICP), which can induce both seizures and hypertension.¹ However, his unremarkable head CT offered no evidence to support a cause for increased ICP, such as a mass or hemorrhage. Additionally, there were no historical or examination concerns for preceding head trauma to suggest a traumatic brain injury.

Other potential causes of new-onset seizures in children were deemed less likely, as they did not explain his hypertension, subacute leg pain, or altered stooling. For example, he lacked fever to support an intracranial infection such as meningitis, encephalitis, or cerebral abscess; his neutrophilic leukocytosis was instead attributed to the profound stress response and peripheral neutrophil demargination that often accompanies afebrile status epilepticus.² Serum chemistries refuted causative metabolic derangements such as hypoglycemia, hyponatremia, and hypocalcemia. Although considered, neuronal migration disorders (eg, lissencephaly, schizencephaly) characteristically present much earlier in life with focal seizures and impaired neurodevelopment, features not present in our patient.³

His unremarkable head CT results and lack of strong evidence for other etiologies for seizure increased our suspicion that his hypertension was not just comorbid with his seizures but instead the direct pathophysiologic cause. Indeed, severe hypertension is a well-known cause of posterior reversible encephalopathy syndrome (PRES), which can manifest as seizures and would also explain his altered mentation.⁴ Given the high concern for PRES in this patient, early consideration for brain magnetic resonance imaging (MRI) would be recommended to aid in diagnostic delineation once the patient is sufficiently stable to undergo the study.

We then shifted our attention to the etiology of his symptomatic hypertension. His degree of hypertension, normal body habitus, and lack of historically elevated blood pressure all favored against a diagnosis of primary hypertension. As such, causes of secondary hypertension were explored with an emphasis on pathologies that might encompass

his nonneurologic symptoms and ambiguous chest x-ray findings.

The causes of pediatric secondary hypertension are numerous and include cardiovascular (eg, aortic coarctation, renal artery stenosis), renal (eg, chronic kidney disease, glomerulonephritis [GN], reflux nephropathy), endocrinologic (eg, hyperthyroidism, Cushing syndrome), intracranial (eg, increased ICP), neoplastic (eg, Wilms tumor, neuroblastoma), and medication-related (eg, psychostimulants, anticholinergic agents, serotonergic agents) etiologies.⁵ His head CT did not support increased ICP or space-occupying lesion as contributing causes. Renal disease was immediately considered higher on the differential diagnosis due to his abnormally high serum creatinine for age and height. Renal pathology can be broadly organized into 3 categories by the site of the primary insult: prerenal, intrinsic, and postrenal. Although prerenal disease infrequently induces hypertension, notable exceptions are renal artery stenosis and fibromuscular dysplasia—conditions that involve abnormalities of the afferent renal vasculature. Regarding intrinsic renal disease, GN is an important consideration for new-onset pediatric hypertension. Given his clinical instability and decreased voiding on the day of presentation, a urine specimen was not initially available to perform a screening urinalysis for GN. However, his examination and radiographs did not show interstitial or pulmonary edema to support the hypervolemic state expected in severe GN. Renal vasculitis, another form of intrinsic renal disease, can occur as a manifestation of systemic vasculitides that are known to cause pulmonary involvement and neuropathic symptoms (eg, granulomatosis with polyangiitis, microscopic polyangiitis)—which offered a potential explanation for his pulmonary opacities and leg pain, respectively.⁶ IgA vasculitis, the most common systemic vasculitis of childhood, was deemed unlikely without intercurrent joint disease, abdominal pain, or purpuric skin lesions.⁷

Postrenal obstruction can present with insidious hypertension. This category can be divided into structural obstruction, such as ureteropelvic junction obstruction, and functional obstruction, such as neurogenic bladder.⁸ If obstructive uropathy were responsible for his hypertension, its co-occurrence with strained defecation could signal a space-occupying intra-abdominal or intrapelvic mass manifesting with direct mass effect, nerve compression, or both. Such a lesion could also produce referred neurogenic pain of the lower extremities and, if neoplastic in nature, lead to radiographically apparent pulmonary metastases. For this reason, early cross-sectional imaging of the abdomen, pelvis, and chest with CT would be indicated; abdominal ultrasound is reasonable to start with if CT is not readily available.

An additional oncologic cause of secondary hypertension is a paraneoplastic syndrome, with specific consideration for underlying neuroblastoma and nephroblastoma (Wilms tumor) in the young pediatric population.

The constellation of new-onset hypertension, renal injury, and seizures can characterize both hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. However, our patient lacked the defining hematologic derangements of hemolytic anemia and thrombocytopenia. Excessive ingestion of psychostimulants, which he was prescribed for ADHD, can cause iatrogenic hypertension but did not explain his numerous other symptoms. Anticholinergic and serotonergic toxidromes are both associated with blood pressure elevation and altered mentation, although he had no history of exposure to common offending medications, such as antiemetics, antipsychotics, and first-generation antihistamines. Hypertension as a result of endocrinologic dysfunction, such as that seen in hypercortisolism, thyrotoxicosis, and hyperaldosteronism, is a final consideration for pediatric secondary hypertension.

Actual Diagnosis

Inadequate control of hypertension with IV hydralazine prompts initiation of an IV nicardipine infusion, producing blood pressure normalization within 30 minutes and accompanying seizure resolution. Shortly after arrival to the PICU, interval abdominal examination reveals progressive bladder distension as well as a large, hard, fixed mass in the patient's left lower quadrant that is both palpable and intermittently visible. Attempts at urinary catheter placement for bladder decompression are unsuccessful due to the catheter meeting resistance. Abdominal ultrasound reveals a large solid pelvic mass measuring at least $11.4 \times 10.5 \times 8.1$ cm, concerning for solid organ neoplasm; mild bilateral hydronephrosis is also present. Immediate transfer to an institution with pediatric oncology and urology services is coordinated. At the receiving institution, CT of the abdomen and pelvis redemonstrates a large pelvic lesion (maximum dimension 15.7 cm), best visualized on subsequent MRI (Figure 3). Results from radiology-guided biopsy return several days after transfer, providing the diagnosis of embryonal rhabdomyosarcoma (RMS). MRI brain, initially deferred due to his tenuous clinical status, demonstrates scattered fluid-attenuated inversion recovery signal hyperintensities of the occipital and parietal lobes of the cerebrum (Figure 4), highly consistent with the pattern of vasogenic edema seen in PRES, thus confirming the suspected etiology of his seizures and mental status changes. Despite our patient's normal head CT, it is crucial to note that PRES can be undetectable on CT in one-quarter of patients with MRI-confirmed disease.⁹ Chest CT reveals

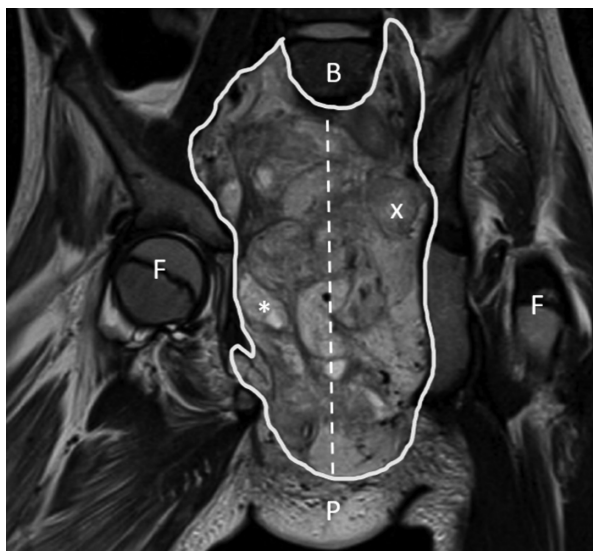


FIGURE 3. Coronal T2-weighted MRI demonstrating large, lobulated, heterogeneously enhancing mass (circumscribed by solid white line) with cephalocaudal diameter of 15.7 cm demarcated by dashed line. The mass extends superiorly to the level of L5 and inferiorly into the perineum (P). Scattered areas of hyper- and hypoenhancement (exemplified by * and x, respectively) throughout the mass are consistent with foci of central necrosis. For additional orientation, the femoral heads (F) and urinary bladder (B) are labeled.

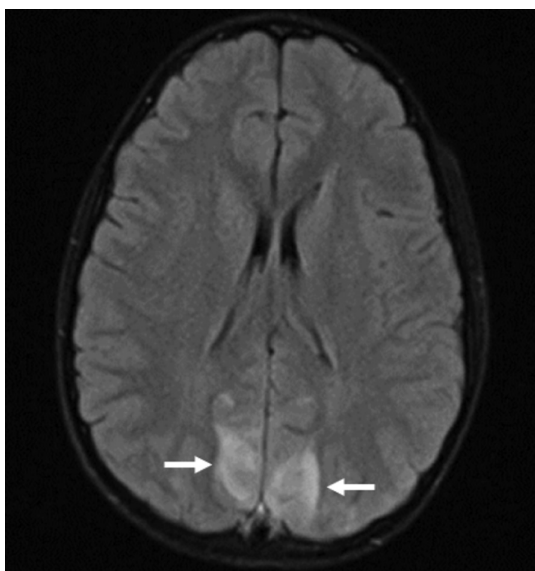


FIGURE 4. Fluid-attenuated inversion recovery sequence MRI of the brain showing hyperintensities involving the bilateral occipital lobes (center-bottom of image, denoted by arrows) consistent with the pattern of vasogenic edema classically seen in posterior reversible encephalopathy syndrome.

innumerable pulmonary nodules representing extensive metastatic disease, corresponding with abnormal lung opacities on initial radiographs (Figure 2). Ultimately, the etiology of his hypertension is attributed to obstructive uropathy.

Although not robustly described in literature, there are indeed case reports of new-onset hypertension related to obstructive uropathy and resultant hydronephrosis, even with unilateral pathology.^{10–15}

The Condition

RMS is a high-grade malignant soft tissue sarcoma, named for its cellular morphology that closely resembles that of striated (skeletal) muscle.^{16,17} Although rare, RMS is the most common soft tissue sarcoma in children and the third most common extracranial solid tumor, constituting approximately 3% of all cancer diagnoses in children under 15 years of age.^{16,18,19} Incidence is highest from birth to 4 years, with nearly two-thirds of pediatric cases occurring by age 10.^{20–22}

The 2 major histologic subtypes are embryonal (ERMS) and alveolar (ARMS), with ERMS representing the large majority of diagnoses and being associated with substantially more favorable outcomes.^{16,17,21–24} The most common sites of primary tumor involvement are the head and neck, genitourinary tract, extremities, and trunk, although any body part can be affected.^{16,22} There are age-related disease patterns, with ERMS and head and neck distribution more common in young children, whereas ARMS and extremity involvement represent a greater proportion of adolescent disease.^{21–24} Metastatic disease at the time of diagnosis is observed in 15% to 20% of patients, with the lung being the most common site of metastasis.^{24,25}

Pelvic RMS and similarly located sarcomas are a diagnostic challenge. The symptomatic course is usually indolent, on the order of months, and is infrequently characterized by the hallmark constitutional symptoms of fever, malaise, anorexia, and weight loss associated with more common childhood cancers, namely hematologic malignancies.²⁶ For abdomino-pelvic RMS, clinical manifestations are typically a result of mass effect. Common gastrointestinal symptoms include abdominal pain and constipation secondary to colorectal compression.^{27,28} Repetitive straining and increased intra-abdominal pressure can lead to rectal prolapse, as seen in our patient. Whereas rectal prolapse in resource-rich countries is typically a result of acute diarrheal illness or chronic constipation, the absence of these features on history should prompt consideration of an alternative pathology. Notably, neurologic and anatomic abnormalities can account for up to 24% of all cases of pediatric rectal prolapse.^{29,30} Similarly, extrinsic compression on the urinary collecting system can produce urinary retention, hematuria, and secondary hypertension.^{10–15,27,28} Direct pressure on the spinal cord or lumbosacral nerves can lead to neuropathic lower extremity pain and weakness as well as neurogenic bowel and bladder dysfunction.^{26,31} Our patient's preceding

hunched posturing was likely a reflexive attempt to alleviate this nerve compression. Like most solid organ tumors, RMS can increase the peripheral leukocyte count via paraneoplastic effect, which may confuse

Treatment/Management

Although slight variation exists between North American and European approaches to treatment, multimodal therapy is the standard of care for RMS, incorporating multiagent chemotherapy, radiation, and, when feasible, surgery.^{16,32,33} Individual therapeutic strategy is heavily influenced by several factors proven to correlate with prognosis including tumor size and anatomic site, histologic subtype, nodal involvement, metastatic disease, and postsurgical residual disease.^{16,22–24,32,34} There is also new understanding of how a tumor's genetic profile, specifically the presence or absence of the *PAX-FOXO1* fusion gene, influences its biologic behavior. This enables finer risk stratification for those with unfavorable histology (ie, ARMS) to better guide management and potentially avoid unnecessarily aggressive treatment.^{35,36}

Induction chemotherapy is started at diagnosis; typical medications include vincristine, dactinomycin, alkylating agents (eg, cyclophosphamide), and doxorubicin. Further chemotherapy may follow depending upon a patient's prognostic group.^{32,37} Primary surgical resection is considered if it permits preserved organ function and does not pose a risk to surrounding structures.^{16,32,38} High-quality adjuvant radiation therapy, started 9 to 12 weeks after chemotherapy initiation, is a mainstay of local control that has been shown to improve treatment outcomes.^{38,39}

Survival rates in pediatric RMS have nearly tripled since regular utilization of chemotherapy began a half century ago.^{20,40} The current 5-year survival rate for all patients is 65%, with extremes of age (less than 1 year, greater than 9 years) associated with worse prognosis.^{20,22–24,41,42} The 5-year event-free survival (EFS), defined as survival without disease progression or recurrence, is particularly good for both low-risk and localized disease (90% and 77%, respectively).^{23,43} Unfortunately, similar trends have not been observed in high-risk (ie, metastatic) disease, in which 3-year EFS remains less than 30%.²⁴ This group serves as a particular focus of current research efforts.^{33,44}

Patient Course

Pediatric urology consultation team successfully placed an indwelling urinary catheter for bladder decompression. Due to strong suspicion for the diagnosis of RMS, the

pediatric oncology consultation team initiated systemic chemotherapy with vincristine, doxorubicin, cyclophosphamide, and dexrazoxane pending the final biopsy results, which confirmed ERMS. Surgical resection was deferred due to tumor site and size. Blood pressure management proved challenging; he required a prolonged IV antihypertensive infusion before de-escalation to oral amlodipine and clonidine patch. His pain was managed with opioids and gabapentin, the latter to address the neurogenic component. He was discharged home in stable condition after 2 weeks. He completed a course of targeted pelvic radiation therapy and is currently completing his eighth cycle of chemotherapy with favorable primary tumor response but ongoing pulmonary metastatic disease. His hydronephrosis resolved on interval imaging. He can void spontaneously although has intermittent urinary incontinence. His hypertension has gradually improved, and he now only requires an intermittent clonidine patch. His course is consistent with the general trend of blood pressure normalization following alleviation of urinary outflow tract obstruction documented in case reports and 1 prospective cohort study.^{10,12–15,45}

LESSONS FOR THE CLINICIAN

RMS is the third-most common extracranial solid tumor in the pediatric population and typically presents with indolent symptoms related to localized mass effect

Presenting symptoms of abdomino-pelvic tumors include abdominal pain, new-onset constipation and urinary retention, and nonspecific lower extremity pain. Most of these are common and usually benign pediatric complaints, meaning a high degree of suspicion is required for diagnosis

Rectal prolapse in the absence of acute diarrheal illness or chronic constipation may suggest neurologic or anatomic abnormalities

Although uncommon, acute hypertensive encephalopathy with secondary PRES is a known etiology for new-onset afebrile seizures in children and can easily be screened for with routine blood pressure measurement at the time of initial assessment

Obstructive uropathy can induce severe, symptomatic hypertension and must be vigilantly monitored for in children with abdomino-pelvic tumors

References for this article can be found at
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Recurrent Fever and Back Pain Associated With Septic Shock in a Healthy 16-Year-Old Girl

Shane D. Falcinelli, PhD,¹ Emma Hignett, MD,² Eric Zwemer, MD,² Patrick O'Shea, MD, MBA^{2,3}

¹Departments of Pathology and Laboratory Medicine, University of California San Francisco, San Francisco, California

²Department of Pediatrics, UNC School of Medicine, Chapel Hill, North Carolina

³Department of Medicine, UNC School of Medicine, Chapel Hill, North Carolina

PRESENTATION

A previously healthy 16-year-old girl presents with a 3-day history of fever, headache, back pain, and dysuria. She also reports nausea, vomiting, and diarrhea. She denies sick contacts, recent travel, or substance use. She endorses sexual activity with consistent condom use, and recently finished her typically regular menses. She is up to date on vaccinations except for the second meningococcal quadrivalent vaccine. She received a filling for dental caries the day before presentation.

She is febrile (maximum temperature [$T_{\max}$] 40.6 °C), hypotensive (blood pressure [BP] of 80/40 mm Hg), tachycardic (heart rate [HR] of 128 beats per minute), and has a respiratory rate of 21 breaths per minute. She is ill-appearing with bilateral costovertebral angle tenderness and generalized erythema. Her oropharyngeal, cardiac, pulmonary, abdominal, and neurologic examinations are unremarkable. A speculum examination demonstrated neither retained hygiene products nor abnormal discharge in the vaginal canal, and cervical motion tenderness is absent. Her initial laboratory evaluation is summarized in Table 1. She remains hypotensive despite 4 L of intravenous (IV) crystalloids and is admitted to the pediatric intensive care unit for septic shock with acute kidney injury requiring initiation of epinephrine.

She receives an extensive workup for sepsis. A computed tomography abdomen and pelvis (CTAP) scan does not show evidence of an acute intra-abdominal process, except for an appendicolith without inflammatory changes. Urine pregnancy test and urine toxicology results are negative. An echocardiogram and ultrasound scan of the bilateral internal jugular veins to evaluate for rheumatic fever and Lemierre syndrome, respectively, are unremarkable. Extensive microbiologic studies are unrevealing (Table 2).

She initially receives vancomycin and piperacillin-tazobactam and is narrowed to piperacillin-tazobactam for presumed pyelonephritis for 48 hours. Her hemodynamics improve, and she is weaned off epinephrine after improvement of her fever and her creatinine over the first 24 hours. On hospital day 2, she reports glossitis with oral pain, which improves over the following week. She is discharged home after resolution of her illness on hospital day 5. Her discharge diagnosis is septic shock of unknown etiology, and she completes a 10-day course of amoxicillin-clavulanate given concern for an odontogenic source from her recent dental filling.

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TABLE 1. Laboratory Evaluations at Time of Initial and Follow-Up Presentations

Laboratory Test Name	Initial Presentation, Day 0	Follow-Up Presentation, Day 31	Conventional Unit Reference Range
WBC	14 000/ μ L (14.0×10^9 /L)	11 100/ μ L (11.1×10^9 /L)	4,200–10 200/ μ L
ANC	13 400/ μ L (13.4×10^9 /L)	9,300/ μ L (9.3×10^9 /L)	2,000–10 100/ μ L
ALC	100/ μ L (0.10×10^9 /L)	600/ μ L (0.60×10^9 /L)	900–4,400/ μ L
Platelets	93×10^3 / μ L (93×10^9 /L)	197×10^3 / μ L (197×10^9 /L)	170 – 380×10^3 / μ L
Creatinine	1.6 mg/dL (141.44 μ mol/L)	0.63 mg/dL (55.69 μ mol/L)	0.37–1.11 mg/dL
AST	52 U/L (0.87 μ kat/L)	8 U/L (0.13 μ kat/L)	13–26 U/L
ALT	39 U/L (0.65 μ kat/L)	10 U/L (0.17 μ kat/L)	12–26 U/L
Total bilirubin	2.8 mg/dL (47.89 μ mol/L)	1.1 mg/dL (18.81 μ mol/L)	0.0–1.2 mg/dL
Lipase	11 U/L (0.18 μ kat/L)	18 U/L (0.30 μ kat/L)	13–80 U/L
Lactate	33.3 mg/dL (3.7 mmol/L)	16.76 mg/dL (1.86 mmol/L)	5–15 mg/dL
CRP	16.4 mg/dL (164 mg/L)	7.4 mg/dL (74 mg/L)	≤ 1.0 mg/dL
Urinalysis	Specific gravity 1.017, 50–100 WBC/lpf, 5–100 RBC/lpf, trace bacteria, 15–25 squamous epithelial/lpf, WBC clumps	Specific gravity 1.016, no other positive cellular contents	

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CRP, C-reactive protein; lpf, low-powered field; RBC, red blood cell; WBC, white blood cell.

She completes her antibiotic course and remains asymptomatic, apart from a desquamating rash shortly after completion. However, 1 month after her initial presentation, she re-presents with fever, neck and back pain, and

TABLE 2. Microbiologic Evaluation During the First Admission

Negative Bacterial Studies
Blood cultures $\times 2$ and urine culture
Urine gonorrhea/chlamydia/trichomonas PCR
Streptococcal antibodies
RPR
Group A <i>Streptococcus</i> rapid antigen and culture
RMSF IgG antibody
Lyme IgM and IgG antibodies
Ehrlichia IgG antibody
Negative viral studies
SARS-CoV2 PCR and nucleocapsid IgG antibody
HIV-1 p24 antigen and HIV-1/HIV-2 antibody
Cytomegalovirus PCR and IgM antibody
EBV IgM and IgG antibodies
Adenovirus and enterovirus PCR
Parvovirus B-19 PCR, IgM, and IgG antibodies
Hepatitis panel
Hepatitis A IgM
Hepatitis B surface antigen
Hepatitis B core IgM
Hepatitis C antibody
Respiratory pathogen panel
Adenovirus
Influenza A
Bordetella pertussis
Coronavirus HKU1
Influenza B
Bordetella parapertussis
Coronavirus NL63
Parainfluenza 1
Chlamydia pneumoniae
Coronavirus 229E
Parainfluenza 2
Mycoplasma pneumoniae
Coronavirus OC43
Parainfluenza 3
SARS-CoV-2 PCR
Metapneumovirus
Parainfluenza 4
Rhino/enterovirus
RSV

Abbreviations: EBV, Epstein-Barr virus; Ig, immunoglobulin; PCR, polymerase chain reaction; RMSF, Rocky Mountain spotted fever; RPR, rapid plasma reagin; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

photosensitivity. She denies dysuria and sick contacts. She has been menstruating for the past 4 days and has been changing her tampon at least once daily.

She is febrile ($T_{\max}$ 38.3 °C), hypotensive (BP 90/50 mm Hg), and slightly tachycardic (HR 102 beats per minute). Her physical examination demonstrates neck stiffness and pain with extension as well as tenderness in her trapezius and latissimus dorsi bilaterally. Her oropharyngeal examination demonstrates tongue erythema with prominent papillae. The remainder of her examination is unremarkable. The initial laboratory evaluation is summarized for comparison in Table 1.

Magnetic resonance imaging scans of the brain and total spine do not demonstrate an etiology of her recurrent neck and back pain. CT chest angiography and CTAP scans to evaluate for pulmonary embolism and acute intra-abdominal process, respectively, are also unremarkable. The patient does not tolerate a lumbar puncture given severe generalized pain; her neck stiffness improves rapidly following the initiation of antibiotics overnight. She is started on ceftriaxone, clindamycin, and vancomycin with significant clinical improvement within 24 hours and discharges on doxycycline on hospital day 4. Additional infectious workup during this admission clarifies the diagnosis.

DISCUSSION

Differential Diagnosis

The differential diagnosis was broad and included localized infection (pyelonephritis, appendicitis, tubo-ovarian abscess, pelvic inflammatory disease, meningitis, or discitis), a systemic infectious process (toxic shock syndrome [TSS], HIV, or Rocky Mountain spotted fever), or an autoimmune process (juvenile idiopathic arthritis or multisystem

inflammatory syndrome in children [MIS-C]). MIS-C was unlikely given the patient's vaccination status and absence of a severe acute respiratory syndrome coronavirus 2 nucleocapsid antibody. Intensive imaging and microbiologic evaluation were unrevealing across both hospitalizations except for a vaginal culture on her second admission, which grew more than 4 methicillin-susceptible *Staphylococcus aureus*.

Actual Diagnosis

She was diagnosed with recurrent TSS. She met the criteria for confirmed TSS per the US Centers for Disease Control and Prevention definition based on history and physical examination (see Table 3).¹ Her menses coinciding with symptom onset for 2 consecutive months was also highly suggestive.

The Condition

TSS is an acute-onset illness consisting of hypotension, fever, rash, and multi-organ system involvement² (Table 3). The annual incidence in the United States is approximately 7 cases per million persons.³ The most common causes of TSS are toxigenic strains of *S. aureus* and *Streptococcus pyogenes*,⁴ which produce several pyrogenic toxins called superantigens.⁴ These superantigens nonspecifically crosslink T cells and antigen-presenting cells, leading to an exuberant inflammatory response and multi-organ dysfunction.⁵⁻⁷ Nearly all menstrual-associated TSS (mTSS) is caused by *S. aureus* strains that produce the superantigen TSS Toxin-1 (TSST-1).⁵⁻⁷ Risk factors for mTSS include tampon and other

intravaginal device use, colonization with TSST-1-producing *S. aureus*, and lack of protective immunoglobulin (Ig) G1 and IgG4 antibody titers against TSST-1.²

These risk factors reflect complex host-pathogen interactions in the presentation of mTSS. Levels of *S. aureus* in the vaginal flora peak during menses, although only a minority of these colonizing strains produce TSST-1.⁸⁻¹⁰ Tampons and other intravaginal devices are thought to modulate levels of oxygen, magnesium, and other physiochemical factors that promote TSST-1 production.² However, mTSS may occur even in the absence of tampon use, suggesting that an intravaginal device is not the sole determinant of mTSS development.

Host immunity also contributes to pathogenesis. Because *S. aureus* is a common colonizer of the nasal cavity, vaginal canal, and human skin, most women are exposed to a TSST-1-producing *S. aureus* strain and develop protective TSST-1 antibodies without developing signs of TSS.¹¹⁻¹⁵ The prevalence of any detectable TSST-1 antibody titer is slightly less frequent in adolescents (80%–90% for adolescents compared with >90% for adult women).^{12,16-18} TSST-1 IgG1 and IgG4 is often low or absent in acute sera from patients with mTSS, suggesting insufficient TSST-1 antibody response as a major risk factor.^{19,20}

The overall recurrence rate of mTSS is approximately 10% to 30% following the index episode.^{2,21,22} In individuals without pre-existing TSST-1 IgG1, there is a low rate of seroconversion following their first episode of mTSS.^{19,23-26} Consistent with this, most recurrent TSS illness occurs in the 1 to 2 months following the initial TSS episode, when

TABLE 3. US Centers for Disease Control and Prevention 2011 Criteria for Toxic Shock Syndrome¹

Clinical Features
1. Fever $\geq 102.0^{\circ}\text{F}$
2. Diffuse macular erythroderma
3. Desquamation 1–2 weeks after the onset of erythroderma
4. Hypotension: SBP 90 mm Hg or less than the fifth percentile by age for pediatric patients aged <16 years
5. Multisystem involvement: 3 or more organ systems affected
Central nervous system: altered mental status
Renal: AKI with BUN or creatinine greater than twice the upper limit of normal for age
Hematology: platelets $\leq 100\,000/\text{mm}^3$
Hepatic: AST, ALT, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age
Muscular: severe myalgias or creatinine phosphokinase level greater than twice the upper limit of normal
Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
Laboratory criteria
Negative blood and/or cerebrospinal fluid cultures (unless positive for <i>Staphylococcus aureus</i>)
Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles
Case classification
Probable: meets all laboratory criteria and 4 of 5 clinical criteria
Confirmed: meets all laboratory criteria and all 5 clinical criteria. If the patient dies before desquamation occurs, they can still meet the confirmed criteria

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, serum urea nitrogen; SBP, systolic blood pressure.

a protective systemic antibody response may have not fully developed.²⁵ The tendency for recurrent TSS to be less severe is consistent with the gradual development of at least partial protective immunity against TSST-1.²⁵

Treatment/Management

Acute management of TSS includes admission to acute or intensive care for fluid resuscitation, antibiotics, and other supportive care.^{2,27} Blood cultures and cultures of the nares, vagina, urine, and other sites as clinically indicated should be collected, and intravaginal or other retained foreign objects should be removed.^{2,27} Beta-lactamase-resistant penicillin should be administered with clindamycin for antitoxin production effect.^{2,27} Vancomycin or linezolid should be added if there is a high suspicion for methicillin-resistant *S. aureus*.^{2,27} Often, broad spectrum antibiotics are indicated when patients with TSS present in undifferentiated septic shock, like our patient. In treatment unresponsive or high-risk patients, the administration of IVIG may improve outcomes through dampening of the superantigen-mediated hyperimmune response.^{2,27} However, there is limited high-quality evidence supporting the efficacy of this intervention, and most studies to date have evaluated IVIG for TSS caused by *Streptococcus pyogenes* rather than *S. aureus*.²⁸

Treatment with antistaphylococcal antibiotics during the first and any subsequent episodes of TSS and discontinuation of tampon use is associated with reduced frequencies of recurrent episodes.^{21,25} Oral contraceptive pill (OCP) use may also decrease risk.² Total body *S. aureus* decolonization with antibacterial soaps, bleach baths, and nasal mupirocin is often performed; however, this has not been rigorously evaluated and decolonization may not be durable.^{29,30}

Patient Course

On her second presentation, our patient received ceftriaxone, vancomycin, and clindamycin empirically and was transitioned to doxycycline on discharge after 48 hours of clinical improvement.

She received a doxycycline refill with instructions to start if her symptoms recurred. She started combined OCPs for suppression of her menses (skipping placebo weeks for full

suppression) and was counseled to discontinue use of all intravaginal devices. She and her family members were instructed to apply nasal mupirocin for a 7-day course to reduce *S. aureus* burden. Postdischarge nasal and vaginal swabs were negative for *S. aureus*.

Despite no known family history of immunodeficiency, Ig levels and childhood vaccine titers were drawn. These were normal except for IgG1 (low at 261 mg/dL (2.61 g/L), reference range 284–772 mg/dL) and IgG4 (low-normal at 6 mg/dL (0.06 g/L), reference range 0.3–111.0 mg/dL). These findings were consistent with the correlation of IgG1 and IgG4 and TSST-1 neutralization.¹⁹ Laboratory evaluation of TSST-1 antibodies was not available at the time of this publication.

Approximately 1 month after discharge, the patient had breakthrough bleeding despite not missing any OCP doses and experienced fever, backache, headache, and nausea. She was not hypotensive, and her symptoms subsided following doxycycline initiation and observation at another hospital. She was using antibacterial soaps and bleach baths but had not been applying nasal mupirocin. Her OCPs were adjusted, and at the time of this report, 7 months after discharge, she has not had a recurrence of TSS.

LESSONS FOR THE CLINICIAN

- Consider TSS as an etiology of unexplained septic shock in healthy adolescent girls, independent of prolonged tampon use.
- Acute management of TSS should focus on source control, fluid resuscitation, and antistaphylococcal antibiotics, including clindamycin, for antitoxin production effects.
- Recurrent menstrual TSS occurs in 10% to 30% of adolescents and young adults following an initial episode; this risk of recurrence can be mitigated with treatment with antistaphylococcal antibiotics during the index episode, menstrual suppression, and on-hand prophylactic antistaphylococcal antibiotics.

References for this article can be found at
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Thrombocytopenia in a Febrile Neonate

Samuel J. Belfer, MD, PhD,^{1,2} Logan Grimes, MD,^{1,3} Lori Handy, MD, MSCE,^{1,3} Stephanie G. Menko, MD^{1,4}

¹Department of Pediatrics, Children's Hospital of Philadelphia, Pennsylvania

²Division of Neurology, Children's Hospital of Philadelphia, Pennsylvania

³Division of Infectious Diseases, Children's Hospital of Philadelphia, Pennsylvania

⁴Division of General Pediatrics, Children's Hospital of Philadelphia, Pennsylvania

PRESENTATION

A 30-day-old healthy female with no medical history presents in February with 1 day of fever of 100.9 °F (38.3 °C) and 3 days of congestion and rhinorrhea. The parents deny their daughter has emesis, diarrhea, or behavior change. She continues to feed well and has normal urine and stool output. She was born at 40 weeks gestation to a G1P1 mother. Prenatal labs were unremarkable, including negative group B *Streptococcus* (GBS), HIV, syphilis, gonorrhea, chlamydia, hepatitis B and C testing, and immunity to rubella and varicella. Pregnancy, delivery, and postnatal course were uncomplicated. The patient received her hepatitis B vaccine at delivery. Her birthweight was in the 75th percentile, and she is growing along her growth curves. She is formula- and breastfed, and her mother takes no medications. She is not in daycare, there are no known sick contacts, and there is no history of travel. The family has a pet dog. She lives in a wooded area of southern New Jersey and spends limited time outdoors.

In the emergency department, her temperature is 102.2 °F (39 °C), heart rate is 185 beats/min, respiratory rate is 58 respirations/min, and blood pressure is 94/45 mm Hg. On physical examination, conjunctivae are clear, and no lymphadenopathy is appreciated. Her lungs are clear to auscultation without focal findings. Her cardiovascular exam reveals a regular rhythm, no murmur, euvoemia, and a normal capillary refill. Her abdominal exam is soft and nontender; her liver is enlarged, with liver edge 2 cm palpated below the costal margin with no splenomegaly. She has no rashes. The initial laboratory assessment is significant for thrombocytopenia ($32 \times 10^9/L$), elevated inflammatory markers (C-reactive protein 6.6 mg/dL; procalcitonin 1.07 ng/mL), normal hemoglobin level (10.9 g/dL, reference range 10.0–18.0 g/dL) and slightly elevated white blood cell (WBC) count ($15.4 \times 10^9/L$, reference range $8.4\text{--}14.4 \times 10^9/L$), with 31% neutrophils and 57% lymphocytes. Liver enzymes are within normal limits (alkaline phosphatase 146 U/L, alanine aminotransferase 43 U/L, and aspartate aminotransferase 127 U/L on a hemolyzed sample). Bilirubin is slightly elevated to 1.8 mg/dL. Coagulation studies are normal (prothrombin time 15.3 seconds, partial thromboplastin time 30.2 seconds). Urinalysis shows negative leukocyte esterase, nitrites, and bilirubin. A lumbar puncture reveals reassuring cerebrospinal fluid (CSF) indices (2 WBC/ μL , 5 red blood cell [RBC]/ μL , glucose 54 mg/dL, total protein 35mg/dL). Respiratory viral panel is negative for COVID-19, respiratory syncytial virus, and influenza. She is admitted and treated with empirical antibiotics of ampicillin and ceftriaxone.

AUTHOR DISCLOSURE: Drs Belfer, Grimes, Handy, and Menko 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.

Blood, urine, and CSF cultures demonstrate no growth at 24 hours. A repeat complete blood count (CBC) finds stable platelets ($35 \times 10^9/L$) with a decrease in hemoglobin (8.0 g/dL) and elevated reticulocytes of 4.2%. A peripheral blood smear is performed. Herpes simplex virus (HSV) and additional viral testing is deferred given early identification of an alternate diagnosis.

DISCUSSION

Differential Diagnosis

The differential diagnosis for this febrile infant with thrombocytopenia included:

Viral infection: Viral infections are thought to account for over half of admissions of febrile neonates in the United States.¹ Even when viral studies are sent, numerous common viruses are unidentified by typical testing paradigms. Viral infection commonly causes fever and upper respiratory symptoms and can cause thrombocytopenia and anemia through bone marrow suppression. Viral etiologies that cause fever and thrombocytopenia include cytomegalovirus, HIV, HSV, and enteroviruses.² Fungal etiologies were considered² but less likely in an immunocompetent, healthy, term neonate.

Bacterial infections: Thrombocytopenia in a febrile infant is concerning for invasive bacterial infection.³ Bacterial pathogens of concern in this age group include GBS, *Staphylococcus aureus*, enteric gram negatives (most commonly *Escherichia coli*), and *Listeria monocytogenes*. Blood, CSF, and urine studies were collected to evaluate these etiologies. Congenital syphilis was in the differential but less likely given the negative maternal serologies. There was no evidence of skin, soft tissue, gastrointestinal, musculoskeletal, or pulmonary focus on physical exam to suggest alternate source of bacterial infection. Disseminated intravascular coagulation (DIC) due to infection was considered as a source of thrombocytopenia, but there were no signs of coagulopathy.

Vector-borne/zoonotic infections: Vector-borne or zoonotic illnesses were considered less likely due to limited exposure history as well as the winter season in the Mid-Atlantic region. With anemia and thrombocytopenia, the differential includes malaria, dengue fever, babesiosis, and toxoplasmosis, depending on an infant's prior exposures and place of birth as well as seasonality of pathogens.

Neonatal alloimmune thrombocytopenia (NAIT): NAIT is the most common cause of severe thrombocytopenia in the neonatal period.⁴ Presenting symptoms include bleeding, petechiae, and purpura, with platelet counts generally below $50,000/\mu L$ ($50 \times 10^9/L$).⁵ Because the pathogenesis

of thrombocytopenia is maternal antibodies to fetal platelet alloantigens,⁶ symptoms and platelet counts typically resolve by 2 weeks of life.⁵ Fever has not been consistently associated with this condition. Malignancy was considered but less likely given the patient's age, excellent growth, and acute presentation.

Actual Diagnosis

The peripheral blood smear revealed intraerythrocytic parasites (Figure 1), consistent with malaria or babesiosis. Thick and thin smear confirmed intracellular parasites with parasite level (percent of infected RBCs) of 8.9% and morphology consistent with *Babesia*. The diagnosis was subsequently confirmed by polymerase chain reaction (PCR).

Further history revealed no travel history to malaria-endemic areas for the mother or the patient. The family lived in a wooded area of southern New Jersey, but the infant had no known tick bites. Mom had a remote history of tick bites prior to pregnancy. She did not have any unexplained fevers, thrombocytopenia, or anemia during pregnancy. The mother did not undergo serologic testing for babesiosis given low clinical utility because this assay does not reliably distinguish acute disease from prior infection. She was asymptomatic, and therefore, treatment would not be indicated. Based on the lack of exposure history in the neonate, birth during winter with low prevalence of ticks in the region, and literature review, a presumed diagnosis of vertically transmitted babesiosis was made.

The Condition

Babesiosis is classically a tickborne illness caused by the protozoan *Babesia microti* and is spread by the tick genus *Ixodes*.⁷ Symptoms typically arise 1 to 4 weeks after tick bite.

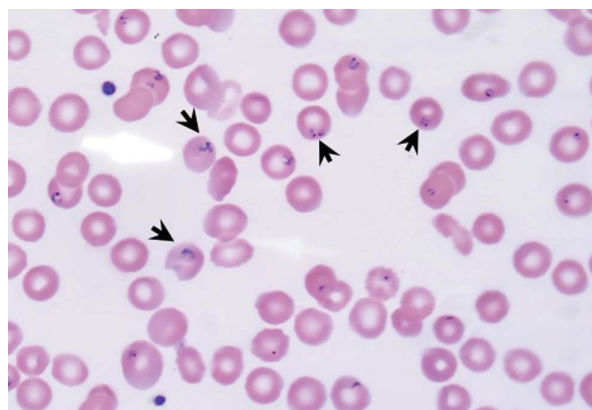


FIGURE 1. Peripheral blood smear of febrile neonate with thrombocytopenia. Intracellular inclusions are noted in numerous erythrocytes (arrows), consistent with *Babesia* infection. The characteristic Maltese cross appearance is present. Giemsa stain, 40× magnification.

TABLE 1. Description of Recorded Cases of Vertical Transmission of Babesiosis

Case Number	Reference	Age of Symptom Onset (d)	Presenting Symptoms	Presenting Hemoglobin (g/dL [$\times 10^{-3}$ g/L])	Presenting WBC ($\times 10^3$ /L)	Presenting Platelet Count ($\times 10^9$ /L)	Parasite Level (%)	Required Transfusion?	Treatment	Treatment Duration
1	Esernio-Jensen et al, 1987 ¹³	30	Fever, irritability, pallor, HSM	9.3	6.5	38	5	Yes	Clindamycin, quinine	10
2	New et al, 1997 ¹⁴	32	Fever, lethargy, poor feeding, pallor, scleral icterus, HSM	10.8	NR	87	4.4	Yes	Clindamycin, quinine, atovaquone	12
3	Sethi et al, 2009 ¹⁵	19	Fever, irritability, pallor, scleral icterus, HSM	8.8	9	34	15	Yes	Atovaquone, azithromycin	10
4	Aderinboye et al, 2010 ¹⁶	27	Fever, pallor	NR	NR	101	2	Yes	Atovaquone, azithromycin	NR
5	Joseph et al, 2012 ¹⁷	41	Fever, irritability, poor feeding, pallor, scleral icterus, HSM	7.1	19.7	100	4	Yes	Atovaquone, azithromycin	9
6	Yager et al, 2014 ¹⁸	34	Fever, fussiness, vomiting, pallor, mottled skin	6.1	8	23	35–40	Yes	Atovaquone, azithromycin, quinine	NR
7	Surra et al, 2015 ¹⁹	26	Fever	6.3	6.3	52	NR	Yes	Atovaquone, azithromycin	NR
8	Saetre et al, 2017 ²⁰	39	Fever, lethargy, pallor, scleral icterus, HSM	8.4	6.5	42	2	No	Atovaquone, azithromycin	15
9	Saetre et al, 2017 ²⁰	18 ^a	Well appearing ^a	13.2	9.7	458	0.5	Yes	Atovaquone, Azithromycin, Clindamycin	14
10	Iyer et al, 2019 ²¹	42 ^b	Fever, congestion, rhinorrhea, lethargy	11.6	7	54	4.8	No	NR	10
11	Handel et al, 2020 ²²	21 ^c	Erythema migrans, lethargy	6.3	10	116	NR, 0.3 ^d	Yes	Atovaquone, azithromycin, clindamycin	10, 42 ^e
12	Reynolds et al, 2020 ²³	40	Fever, fussiness	10.3	7.5	41	3.6	No	Atovaquone, azithromycin	14
13	Belfer et al, 2023	30	Fever, rhinorrhea, congestion, hepatomegaly	10.9	15.4	32	8.9	Yes	Atovaquone, azithromycin	14

Abbreviations: HSM, hepatosplenomegaly; NR, not recorded; PCR, polymerase chain reaction.

^aAsymptomatic at time of presentation.

^bAge reported in weeks in original publication.

^cPositive *Babesia* PCR. Asymptomatic at time of positive PCR result.

^dParasite level after initial treatment course of 10 d of atovaquone and azithromycin.

^eReceived 2 distinct treatment courses: first course of atovaquone and azithromycin and second course with all 3 listed antimicrobials.

Fever and fatigue are the most common symptoms of *Babesia* infection; hemolytic anemia, thrombocytopenia, and hepatosplenomegaly are also common.^{8,9} Anemia and thrombocytopenia are secondary to innate immune response to infection and cell lysis, while hepatosplenomegaly is secondary to sequestration of infected cells.⁹ While most pediatric cases have mild symptoms, severe manifestations in older adults or immunocompromised individuals include acute respiratory distress syndrome (ARDS), DIC, and prolonged relapsing course despite antibiotic therapy.⁹ The endemic region for *B. microti* lies in the Northeastern and Northern-Midwestern regions of the United States during warm spring and summer months and has rapidly expanded southward to Florida and westward to South Dakota over the last decade.¹⁰

PCR is the diagnostic gold standard, but peripheral blood smear can reveal intracellular inclusions that form a “Maltese cross,” the hallmark pathologic finding of babesiosis (Figure 1). As in this case, this finding often precedes PCR results and is a helpful diagnostic tool. Serial parasite levels are helpful to evaluate effectiveness of antimicrobials and correlate with clinical status.

Vertical transmission of *Babesia* infection has been appreciated as an additional route of infection in mammals.^{7,11,12} This case represents the 13th reported case of congenital babesiosis in the literature^{13–23} (Table 1). The most common presenting findings are fever (12/13, 92% of cases) and thrombocytopenia (12/13, 92%), with fewer patients presenting with anemia (6/13, 46%). Severity of anemia and thrombocytopenia did not correlate with parasite load when analyzed across all cases. Severe sequelae of babesiosis were not observed in congenital cases, with no documented cases of ARDS, DIC, or splenic rupture.

Vertical transmission occurs via transplacental spread from mother to fetus. While this case had no confirmed maternal infection, asymptomatic parasitemia occurs in endemic areas.²⁴ One study found *B. microti* antibodies in 1% of all healthy, asymptomatic blood donors, with more than half of seropositive donors having active parasitemia.²⁴ Notably, the age of presentation of symptomatic infants with congenital babesiosis is between 19 and 42 days of life, regardless of timing of maternal infection, while congenital malaria typically presents earlier at 10 to 30 days of life.²⁵ This may reflect differences in mechanism of neonatal infection or virulence of these parasites; further investigation is necessary to elucidate this phenomenon.

Treatment/Management

While babesiosis can be a self-limited illness in children and adults, the illness course appears more severe in infants. More than 80% of documented cases of vertically transmitted babesiosis have required packed RBC transfusion to treat severe anemia (Table 1). Antimicrobial treatment regimens for symptomatic *Babesia* infection have evolved. While early reports utilized clindamycin and quinine,^{13,14,18} consensus guidelines now recommend atovaquone and azithromycin because this regimen has a more favorable side-effect profile and remains effective.²⁶ While the use of azithromycin in infants younger than 6 weeks old has been associated with infantile hypertrophic pyloric stenosis, the risks and benefits were weighed in this case and deemed acceptable for use.

Patient Course

Treatment with azithromycin and atovaquone was initiated. Her anemia worsened with lowest recorded hemoglobin of 6.7 g/dL. She required two 10 mL/kg (1×10^{-2} L/kg) packed RBC transfusions. Her platelet levels remained stable without platelet transfusions. On day 7 of treatment, laboratory studies demonstrated stabilizing hemoglobin, normal platelet level, and undetectable parasite levels on peripheral blood smear, and she was discharged home. She completed a total 14-day antimicrobial course, with undetectable parasite levels and reassuring CBC parameters at 4-week follow-up.

LESSONS FOR THE CLINICIAN

- Thrombocytopenia in febrile neonate should prompt a broad differential diagnosis beyond typical bacterial and viral pathogens; a peripheral blood smear can be an important diagnostic test in these cases.
- History of maternal tick exposure should prompt consideration of testing for *Babesia* infection in an infant with fever and thrombocytopenia.
- Management of neonatal babesiosis includes antibiotics and supportive care, including blood component transfusions as clinically indicated.

Acknowledgments

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An Unusual Cause of Bone Pain in a 3-Year-Old Girl

Stephanie S. Squires, MD, Megan Faughnan, MD

Division of Hospital Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California

PRESENTATION

A 3-year-old previously healthy female with history of a cow's milk allergy presents to the emergency department with a 2-week history of intermittent leg pain, chapped lips, and decreased oral intake. Her mother states that 2 weeks ago she noticed that her daughter had chapped lips and was eating less frequently. One week ago, she also developed an intermittent, pruritic rash on her arms that improved with cetirizine. She acutely became more tired 2 days prior to presentation and was refusing to walk or stand, prompting a visit to the emergency department for further evaluation.

She does not take any medications other than a daily multivitamin. She follows a dairy-free diet and drinks up to 3 cups of rice milk per day. The patient has been afebrile. There is no known trauma or recent infections. Review of systems is negative for vision or hearing changes, shortness of breath, increased thirst, nausea, vomiting, diarrhea, or constipation. Other than expressive speech delay, developmental milestones are appropriate for age.

Her vital signs are within normal limits. She weighs 11.9 kg (seventh percentile), with a body mass index of 13 kg/m² (0.3 percentile). On physical exam she is tired but nontoxic appearing. She has dry mucous membranes and cheilitis. Her lower extremities are tender to palpation, and she is unwilling to bear weight. A pruritic, erythematous, blanching, maculopapular rash is present along the posterior trunk and several excoriation marks are noted on her upper arms, back, and abdomen. Heart, lung, and abdominal exams are unremarkable.

Initial laboratory results (Table 1) reveal an elevated calcium at 13.1 mg/dL (8.8–10.8 mg/dL) with an ionized calcium of 1.68 mmol/L (1.12–1.32 mmol/L). Phosphate is 5.8 mg/dL (3.2–5.5 mg/dL). Erythrocyte sedimentation rate (ESR) is 30 mm/h (0–10 mm/h) and C-reactive protein is 0.3 mg/dL (<0.5 mg/dL). Complete blood count is normal. An electrocardiogram is obtained and is normal. Because of her level of hypercalcemia, a baseline renal ultrasound is obtained and demonstrates medullary nephrocalcinosis. Given the patient's elevated calcium level, she is admitted for further workup and management.

DISCUSSION

Differential Diagnosis

The differential diagnosis for hypercalcemia is broad. Potential causes of hypercalcemia include mechanisms that lead to increased bone resorption, increased gastrointestinal absorption of calcium, and decreased renal excretion of calcium.¹ A summary of a diagnostic pathway for hypercalcemia is provided in Figure 1.

Parathyroid hormone (PTH), calcitriol (vitamin D:1,25 OH), and calcitonin are responsible for calcium homeostasis in the body. Once hypercalcemia is identified

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

TABLE 1. Laboratory Workup

Test	Value	Reference Range
White blood cell, K/uL	15.1	6.0–17.0
Hemoglobin, g/dL	11.9	3.90–5.30
Hematocrit, %	37	34.0–40.0
Platelets, K/uL	292	150–400
Sodium, mmol/L	141	135–145
Potassium, mmol/L	3.6	3.5–5.5
Chloride, mmol/L	106	98–107
Carbon dioxide, mmol/L	21	22–29
Blood urea nitrogen, mg/dL	12	9–18
Creatinine, mg/dL	0.40	0.26–0.42
Glucose, mg/dL	144	70–100
Ionized calcium, mmol/L	1.68	1.12–1.32
Calcium, mg/dL	13.1	8.8–10.8
Total protein g/dL	6.1	5.7–8.0
Albumin, g/dL	3.4	3.8–5.4
Total bilirubin, mg/dL	0.6	<1.0
Alkaline phosphatase U/L	403	142–335
AST U/L	90	<77
ALT U/L	41	10–35
Phosphorus, mg/dL	5.8	3.2–5.5
Magnesium, mg/dL (mmol/L)	2.0	1.7–2.3
ESR, mm/hr	30	0–10
CRP, mg/dL	0.3	<0.5
PTH, pg/dL	6.4	15.0–65.0
Calcium/creatinine ratio, mg/g	1377.0	<400.0
PTH-related peptide, pmol/L	1.1	<4.2
Vitamin D (25 OH), ng/mL	46	25–80
Vitamin D (1,25 OH), pg/mL	10	20–70
TSH, uIU/mL	0.25	0.7–5.90
T4, ng/dL	1.33	0.80–1.75
Urine catecholamines (epinephrine), mcg/g creat	<15	4–32
Urine catecholamines (norepinephrine), mcg/g creat	<31	20–108
Urine catecholamines (dopamine), mcg/g creat	311	295–1123
Vitamin A, ug/dL	89	20–43

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; creat, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PTH, parathyroid hormone; TSH, thyrotropin.

in a patient, the first step is to identify the level of PTH. A normal or increased PTH may point toward a differential diagnosis of familial hypocalciuric hypercalcemia or primary hyperparathyroidism respectively. The patient's PTH is low at 6.4 pg/mL (15.0–65.0 pg/mL) and urinary calcium/creatinine ratio is 1377.0 mg/g (<400.0 mg/g), suggesting against both primary hyperparathyroidism and familial hypocalciuric hypercalcemia.

In normal homeostasis, PTH secretion is sensitive to changes in serum calcium levels, with increased calcium levels inhibiting PTH release.² Given that our patient's PTH levels were appropriately low, the next step is to determine the level of parathyroid related peptide (PTHrP). PTHrP can be ectopically secreted by malignant tumors and mimics biologic effects of PTH leading to paraneoplastic hypercalcemia.^{1,2} If PTHrP is normal or low however,

the differential then includes vitamin D toxicity, vitamin A toxicity, granulomatous disease, hyperthyroidism, and pheochromocytoma.

A PTHrP laboratory is performed. However, this laboratory test typically takes up to 5 days to determine a result, so in the meantime a broad workup is pursued. The elevated ESR noted on admission is thought to be secondary to an inflammatory state from hypercalcemia.³ Otherwise, in our patient, thyrotropin (TSH) is low at 0.25 uIU/mL (0.7–5.90 uIU/mL) and T4 is normal at 1.33 ng/dL (0.80–1.75 ng/dL), ruling out hyperthyroidism. Bilateral lower extremity imaging is obtained, which demonstrates dense metaphyseal bands seen in vitamin D toxicity, abnormalities in calcium-phosphate homeostasis, or malignancy (Figure 2).⁴ Vitamin D (25 OH) is normal at 46 ng/mL (25–80 ng/mL) and vitamin D (1,25 OH) is low at 10 pg/mL (20–70 pg/mL), ruling out vitamin D toxicity and granulomatous disease respectively. To screen for malignancy, a chest x-ray is obtained, which is normal. Lactate dehydrogenase and uric acid studies are normal. Urine catecholamines are within normal limits, suggesting against pheochromocytoma. Ultimately, PTHrP is low at 1.1 pmol/L (<4.2 pmol/L).

Actual Diagnosis

The patient is found to have an elevated vitamin A level of 80 µg/dL (11.3–64.7 µg/dL). Additional nutrition history identified that the patient drinks 12 oz of rice milk per day (which contains 90 µg of vitamin A/oz) and therefore averages up to 1080 µg of vitamin A daily. The recommended daily dose of vitamin A for her age is 300 µg.^{3,5,6} In addition, her grandmother also allows her to eat as many gummy vitamins as she desires and describes that she eats them “like candy.” Further inquiry does not reveal that the patient has access to any other medications. She is diagnosed with vitamin A toxicity as the cause of her hypercalcemia.

The Condition

Vitamin A toxicity is a rare entity with few case reports represented in the literature.^{3,5} Vitamin A is a fat-soluble compound that is essential for growth, bone health, vision, and cell differentiation, and can only be acquired by diet.⁷ Vitamin A has a long biological half-life and accumulates in adipose tissue. Given that it is rapidly absorbed and slowly cleared, vitamin A toxicity can either be due to a large ingestion of vitamin A causing acute toxicity or chronic toxicity after prolonged intake of several doses.^{5,7} Signs and symptoms of vitamin A toxicity include headaches, nausea, vomiting, cheilitis, abdominal pain, rash, pruritus, bone pain, dysuria or polyuria, dizziness, and altered mental status.⁷ At toxic levels, vitamin A can also lead to bone resorption ultimately leading to hypercalcemia, though the mechanism is

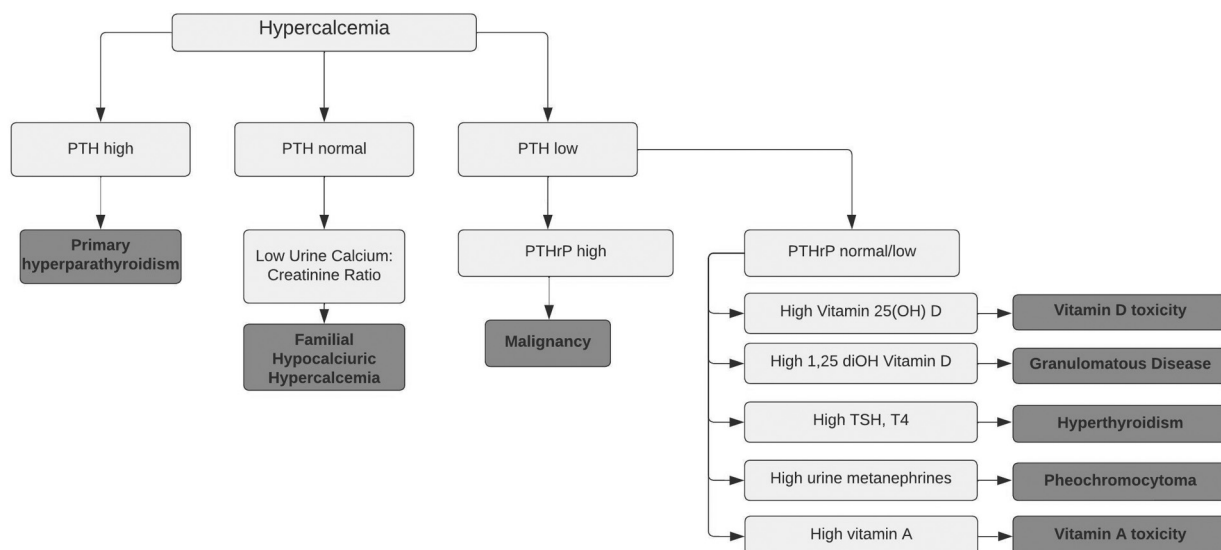


FIGURE 1. Causes of hypercalcemia and diagnostic pathway.
Abbreviations: PTH, parathyroid hormone; PTHrP, parathyroid related peptide; TSH, thyrotropin.

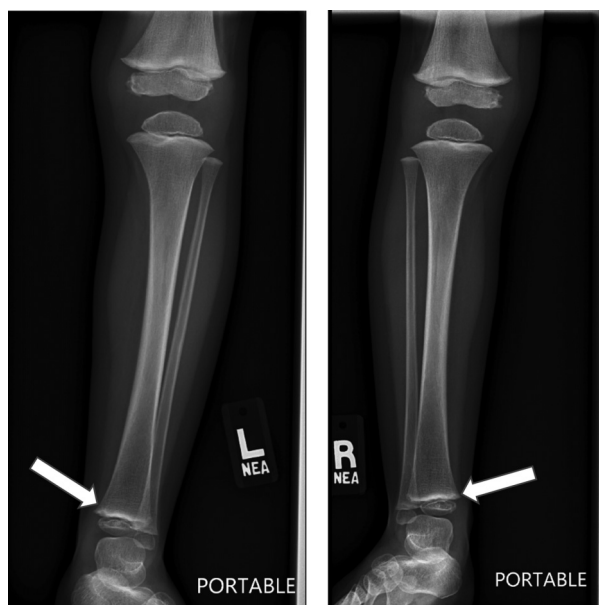


FIGURE 2. Bilateral lower extremity x-ray. Diffusely dense metaphyseal bands.

not well understood.⁵ Therefore, some symptoms present in vitamin A toxicity may also overlap with those present in patients with hypercalcemia. Additionally, excess vitamin A is associated with development of idiopathic intracranial hypertension, papilledema, and elevated triglycerides, which in turn may cause elevated liver enzymes as seen in this patient.⁷ Excess vitamin A is stored in stellate cells in the liver and accumulation can lead to their activation leading to liver injury.⁸

Management

The management of vitamin A toxicity starts with discontinuing further consumption of vitamin A. Given that vitamin A is stored in adipose tissue and is slowly cleared, close follow-up is needed to monitor the trend in levels.⁷

Next, hypercalcemia secondary to vitamin A toxicity needs to be addressed. Treatment of hypercalcemia depends on the severity of the hypercalcemia as well as the symptoms the patient experiences.^{1,9,10} Hypercalcemia is classified as mild (Ca <12 mg/dL), moderate (Ca 12–14 mg/dL), or severe (Ca >14 mg/dL).¹ Mild hypercalcemia does not necessarily require treatment if the patient is asymptomatic. Signs and symptoms of hypercalcemia include nephrocalcinosis, bone pain, nausea, vomiting, constipation, abdominal pain, neuropsychiatric manifestations (such as lethargy, confusion, or fatigue), muscle weakness, and cardiac arrhythmias.^{1,9}

The goals for treatment of hypercalcemia include stabilizing and reducing the calcium level with adequate hydration, increasing urinary calcium excretion, and inhibiting osteoclast activity in the bone.⁵ Therefore, the first step is to give intravenous hyperhydration, sometimes necessitating up to 2 times the maintenance fluid rate to achieve effect. If during treatment there is concern for fluid overload, diuretics such as furosemide may be needed to help with renal filtration of calcium. For some patients, hyperhydration is enough to correct hypercalcemia. Patients with symptomatic moderate hypercalcemia and severe hypercalcemia, regardless of symptoms, require more aggressive treatment and will need medications such as calcitonin or bisphosphonates to inhibit further osteoclastic resorption to correct the hypercalcemia.^{1,5,11} Calcitonin is

approved for children to treat acute refractory hypercalcemia and was our choice because of its rapid onset of action; however, tachyphylaxis occurs quickly and persistent hypercalcemia will require bisphosphonate therapy. These are all temporizing measures and once the underlying etiology is resolved, the patient's calcium levels will also return to normal.

Patient Course

Our patient's primary signs and symptoms from her hypercalcemia included bone pain, abdominal pain, decreased oral intake, and fatigue. Her initial calcium level was 13.1 mg/dL, placing her in the category of symptomatic moderate hypercalcemia. She was hyperhydrated with intravenous fluids running at 2 times her maintenance rate. Given her persistent hypercalcemia and worsening renal function, she was given a single dose of calcitonin (4 units/kg). This ultimately allowed her corrected calcium to stabilize at 11.7 mg/dL the following day. She started to have improved energy and oral intake and was able to stand prior to discharge.

In the setting of her vitamin A toxicity, she was also found to have hypertriglyceridemia of 136 mg/dL and elevated liver enzymes with aspartate aminotransferase (AST) at 107 U/L. Prior to discharge, she was evaluated by ophthalmology for a routine eye exam and did not have papilledema from her

vitamin A toxicity. Prior to discharge, her family was provided with a list of vitamin A rich foods to avoid (such as carrots, leafy green vegetables, and fortified milk).

After 1 month of avoiding vitamin A intake, her calcium leveled to 9.5 mg/dL (8.8–10.8 mg/dL) and her vitamin A level was normal at 38 µg/dL (11.3–64.7 µg/dL). Her creatinine returned to normal to 0.27 mg/dL (0.26–0.42 mg/dL) and AST returned to 61 U/L (<77 U/L). Additional follow-up studies, including TSH and T₄, were normal. One month after discharge, her energy level had improved, her bone pain had resolved, and she was able to ambulate without issue.

LESSONS FOR THE CLINICIAN

- Vitamin A toxicity is a potential cause of hypercalcemia and can present with leg pain, pruritus, rash, and cheilitis.
- Vitamin A toxicity sequelae include idiopathic intracranial hypertension, papilledema, and hypertriglyceridemia.
- Hypercalcemia treatment is guided by the severity of the calcium level and presence of symptoms and may include interventions such as intravenous hydration, diuretics, and medications that inhibit osteoclast activity in the bone.

References for this article can be found at
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Development and Pediatric Use of the 20-Valent Pneumococcal Conjugate Vaccine

Eva R. Johnson, MD,^{1,2} Miriam A. Stats, MD,¹ Douglas Fleck, MD^{1,2}

¹Rainbow Babies & Children's Hospital, Cleveland, Ohio

²Case Western Reserve University, Cleveland, Ohio

UPDATED 2023 PNEUMOCOCCAL VACCINE RECOMMENDATIONS

The Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends pneumococcal vaccination for all children younger than 5 years, for people aged 5 to 64 years with high-risk conditions (see Table 1), and for all adults 65 years or older. In 2021 ACIP approved a 20-valent pneumococcal conjugate vaccine (PCV20 [Pneumovax 20]) for use in adults aged 19 to 64 years with high-risk conditions, and all adults 65 years or older. In June 2023, ACIP expanded their recommendation for use of PCV20 (as an optional alternative to 15-valent pneumococcal conjugate vaccine (PCV15 [Vaxneuvance]) for routine vaccination of children younger than 5 years and children between ages 2 and 18 years with high-risk conditions. This guidance also expanded high-risk conditions to include moderate persistent and severe persistent asthma, chronic liver disease, and chronic kidney diseases beyond nephrotic syndrome and maintenance dialysis.

Background

The discovery of *Streptococcus pneumoniae*, a gram-positive, aerobic diplococcus, dates back to 1881, when Louis Pasteur first isolated it from a patient with rabies. *S. pneumoniae* spreads through respiratory droplets and asymptotically colonizes the upper respiratory tract of more than 50% of children younger than 5 years, decreasing to colonization rates of 5% to 10% in adults. Children younger than 5 years and adults 65 years or older have the highest risk for pneumococcal disease. *S. pneumoniae* causes a spectrum of illness from noninvasive diseases, including otitis media, sinusitis, and community-acquired pneumonia, to invasive pneumococcal diseases (IPD) including meningitis, bacteremia, osteomyelitis, and pneumonia with bacteremia. In the United States, *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia in children younger than age 5 years (second to *Mycoplasma pneumoniae* in older children) and the most common cause of bacterial meningitis in children ages 2 months to 11 years. There are over 100 *S. pneumoniae* serotypes. Most serotypes have a polysaccharide capsule, which helps them evade some human immune defenses. Differences in the capsule polysaccharide are often the basis for serotype classification and primarily influence the virulence of the serotype.

Vaccine Development

Efforts to develop a pneumococcal vaccine started more than 100 years ago when British physician Sir Almroth Wright developed a whole-cell vaccine to prevent

AUTHOR DISCLOSURE: Drs Johnson, Stats, and Fleck 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.

Recommendations for Use of 20-Valent Pneumococcal Conjugate Vaccine in Children - United States, 2023. Updates ACIP. *MMWR Morb Mortal Wkly Rep.* 2023;72(39):1072. doi: 10.15585/mmwr.mm7239a5

Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases.* Hall E, Wodi AP, Hamborsky J, et al, eds. 14th ed. Public Health Foundation; 2021.

The Remarkable History of Pneumococcal Vaccination: An Ongoing Challenge. Musher DM, Anderson R, Feldman C. *Pneumonia (Nathan).* 2022;14(1):5. doi: 10.1186/s41479-022-00097-y

TABLE 1. Conditions at High Risk for Pneumococcal Disease

Chronic Medical Conditions	Immunocompromising Conditions
Cerebrospinal fluid leak	Maintenance dialysis
Chronic heart disease	Nephrotic syndrome
Chronic kidney disease (except as otherwise specified with immunocompromising conditions)	Congenital or acquired asplenia or splenic dysfunction
Chronic liver disease	Congenital or acquired immunodeficiency
Chronic lung disease (including moderate persistent or severe persistent asthma)	Treatment with immunosuppressive drugs or radiation therapy
Cochlear implant	Solid organ transplant
Diabetes mellitus	HIV infection
	Sickle cell disease or other hemoglobinopathy

pneumococcal pneumonia in South African gold miners. By the 1940s, 2 pneumococcal vaccines were commercially available. However, with the discovery of penicillin, the interest and investment in a pneumococcal vaccine waned and it was deemed obsolete in the antibiotic age, and the pneumococcal vaccines were removed from the market. Despite the use of penicillin, case-fatality rates from *S. pneumoniae* remained high. Hence, a group of researchers, motivated by a desire to decrease IPD, developed the 14-valent polysaccharide vaccine, which was licensed in the United States in 1977. In 1983, the 23-valent polysaccharide vaccine (PPSV23) replaced the 14-valent vaccine and was recommended only for patients aged 2 years and older with specific high-risk conditions. While effective in older children and adults, *unconjugated* vaccines such as PPSV23, which rely on a T-cell independent immune response, are ineffective in children younger than 2 years due to lack of immune system maturity. Given that children younger than 2 years are at highest risk for pneumococcal disease, researchers continued to pursue a pneumococcal vaccine that would be effective across the age spectrum, from infants to adults. In 2000, the United States licensed the first *conjugate* pneumococcal vaccine, Prevnar 7 (PCV7).

For conjugate pneumococcal vaccines, the pneumococcal polysaccharide of each included serotype is attached to an immunogenic protein—specifically, a genetically detoxified diphtheria toxin, which promotes both B lymphocyte and T lymphocyte enlistment. Conjugate vaccines produce a more robust and long-lasting immune response than unconjugated pneumococcal vaccines and are effective in children younger than 2 years. Prior to PCV7, there were approximately 17 000 pediatric cases of IPD and 200 deaths annually in the United States. After adoption of PCV7,

nasopharyngeal colonization and noninvasive disease from PCV7 serotypes significantly decreased and cases of invasive disease from PCV7 serotypes declined by more than 80% among children younger than 5 years. Under pressure from broadening vaccine coverage, *S. pneumoniae* has adapted to evade the immune response through serotype replacement, in which serotypes not included in vaccines become more prevalent, and by capsular switching, in which serotypes adapt their capsular types to nonvaccine capsules. Also, as pneumococcal vaccines decrease infection rates of covered serotypes, other uncovered serotypes become more prevalent, which has prompted vaccine developers to add new serotypes to pneumococcal vaccines. In 2010, PCV13 replaced PCV7; in 2022, PCV15 was approved for children; and in 2023, PCV20 became the newest pediatric pneumococcal vaccine. Once PCV20 was approved, the ACIP no longer recommended PCV13 for routine immunization, instead recommending either PCV15 or PCV20. When looking at IPD in US children younger than 5 years, researchers predict that PCV15 and PCV20 will protect against an additional 17% and 39% of cases, respectively, in comparison to PCV13.

The ACIP used the Grading of Recommendations, Assessment, Development and Evaluation framework to evaluate PCV20 and determined that there was moderate evidence for approval both for efficacy and for safety. No published disease outcome studies were available to assess efficacy, so approval was based on immunogenicity studies. The immune response from PCV20 was slightly lower compared with PCV13 for the same 13 serotypes, but the clinical significance of this finding is unknown. Safety studies had limited sample sizes, but there were no vaccine-related serious side effects. PCV20 is contraindicated in anyone with a prior severe allergic reaction after a conjugate pneumococcal vaccine or to any vaccine containing diphtheria toxoid, or in anyone with a severe allergy to any component of PCV20.

Summary Recommendations for Children

The ACIP recommends routine pneumococcal conjugate vaccination using either PCV15 or PCV20 for all children younger than 5 years:

- Routine schedule: Administer 4 doses of PCV15 or PCV20 to infants/toddlers at ages 2 months, 4 months, 6 months, and 12 through 15 months.
- Catch-up schedule: Administer PCV15 or PCV20 per CDC catch-up schedule to vaccinate children younger than 5 years who are unvaccinated or not fully vaccinated. The number of catch-up doses and dose schedule depend on the current age of the child and timing of any prior doses. Given the complex rules with pneumococcal vaccination, the CDC

developed the *PneumoRecs VaxAdvisor* mobile app and website (<https://www2a.cdc.gov/vaccines/m/pneumo/pneumo.html>) to provide patient-specific guidance.

Children aged between 2 and 18 years with certain high-risk conditions (Table 1) will need additional pneumococcal vaccine doses if their routine vaccinations did not include PCV20, and depending on whether they received PPSV23. Again, the *PneumoRecs VaxAdvisor* mobile application and website can provide patient-specific guidance.

Despite the effectiveness of pneumococcal vaccination in preventing disease, there are substantial inequities in pneumococcal vaccination rates. Vaccination rates are below the national average for children younger than 2 years who live in poverty, have Medicaid or no insurance, or are Black, American Indian, or Alaskan Native. Providers may consider increased vaccine outreach in these groups. In addition, given that people with moderate persistent or severe persistent asthma are now considered high-risk for pneumococcal disease, it may be helpful for clinics to implement processes to identify these patients and target them for recommended PCV20 or PPSV23 immunization.

Comments. Prior to the development of pneumococcal vaccines, many of my patients suffered morbidity from *S. pneumoniae*

infections. Many health care visits involved treating infants/children with otitis media and community-acquired pneumonia, obtaining blood cultures to evaluate for potential *S. pneumococcal* bacteremia, and performing lumbar puncture procedures to evaluate for meningitis. I still remember many of the patients I cared for who suffered significant sequelae from *S. pneumococcal* infections: bacterial meningitis, neurological damage, permanent hearing loss, and even death. Yet what an amazing journey to witness the incredible benefit from continued research on pneumococcal vaccines and to observe how meningitis from this pathogen has become a much rarer event. I express gratitude to the many researchers who contributed to the development of pneumococcal vaccines, for their ongoing research efforts to continuously improve these vaccines, and now for the current benefit to patients across the life trajectory. When we look at the inequities of pneumococcal vaccine receipt, all of us as pediatricians must continue to advocate for equal access to these vaccines, minimize barriers to vaccine receipt, and strive to develop trust with parents to minimize and eliminate any vaccine hesitancy that may exist.

Janet R. Serwint, MD
Associate Editor, In Brief



Monoclonal Antibody Therapies for Children

Shardhat Daggumati, MD, John C. Carlson, MD, PhD

Department of Pediatrics, Ochsner Health System, New Orleans, Louisiana

Monoclonal antibodies are produced by transformed cell lines, engineered to create antibodies with a uniform specificity. Because monoclonal antibodies are derived from a living source, they are designated as biologic medications and provided through specialty pharmacies able to facilitate the dispensing of these medications. The effectiveness of monoclonal antibody therapies is dependent on the ability of the antibody's antigen-binding fragment (Fab) portion to target a specific epitope, typically neutralizing a key function of a protein by binding to it. Because monoclonal antibodies can neutralize a broad range of antigens, they have been used to neutralize infectious pathogens as well as target human proteins implicated in disease, including cancers, allergic disease, and autoimmune conditions.

In addition to neutralizing the function of proteins through binding, the crystallizable fragment (Fc) region of antibodies can increase destruction of target cells by activating complement and by facilitating opsonization by phagocytes after binding. Additional mechanisms for destroying target cells include the addition of toxins to the monoclonal antibody and the use of "bispecific" antibodies that use 2 different Fab arms, useful for linking 2 targets together. Adjustments of the Fc portion of the antibody can also alter the stability, activity, and longevity of the medication.

Once a monoclonal antibody is developed, it becomes easily scaled up in laboratories. This contrasts with polyclonal antibodies that are derived from whole organisms, such as humans immunized with rabies virus to produce the human rabies immunoglobulin products used for postexposure prophylaxis. The uniformity of the monoclonal antibody target is also useful for the potential to elicit a uniform response. The response varies by specific epitope binding on the target antigen, with minor changes making a clinically meaningful difference.

There are currently 46 monoclonal antibody products labeled for use in children (Table 1). The first Food and Drug Administration (FDA) approval of a monoclonal antibody therapy was for muromonab in 1986, a mouse-derived antibody targeting the cluster of differentiation (CD) 3 complex on T cells to prevent transplant rejection. The only other mouse-derived monoclonal antibody approved by the FDA for use in children is isblinatumomab, a bispecific monoclonal antibody that targets both CD3 on T cells and CD19 on B cells, leading to T cell-initiated apoptosis of the B cell once both are bound. Mouse-derived proteins can elicit human immune responses. Therefore, most monoclonal antibodies used as medication include human DNA (DNA). Fully human antibodies are denoted with the suffix -umab. Monoclonal antibodies with the complementary-determining region of DNA derived from an animal model, spliced into DNA that otherwise encodes production of a human antibody, are called humanized monoclonal antibodies and denoted with the suffix -zumab. Monoclonal antibodies produced by human-mouse chimeric cells are denoted with the suffix -ximab. These are generally well tolerated;

AUTHOR DISCLOSURE: Dr Daggumati and Dr Carlson have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Lower Use of Biologics for the Treatment of Asthma in Publicly Insured Individuals. Akenroye AT, Heyward J, Keet C, Alexander GC. *J Allergy Clin Immunol Pract.* 2021;9(11):3969–3976. PubMed doi: 10.1016/j.jaip.2021.01.039

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Dynamics of Patents, Orphan Drug Designation, Licensing, and Revenues from Drugs for Rare Diseases: The Market Expansion of Eculizumab.

Caetano R, Cordeiro Dias Villela Correa M, Villardi P, Almeida Rodrigues PH, Garcia Serpa Osorio-de-Castro C. *PLoS One.* 2021;16(3):e0247853. PubMed doi: 10.1371/journal.pone.0247853

La Rev Stat §22:1060.8 (2023)

Global Impact of Monoclonal Antibodies (mAbs) in Children: a Focus on Anti-GD2. Larrosa C, Mora J, Cheung NK. *Cancers (Basel).* 2023;15(14):3729. PubMed doi: 10.3390/cancers15143729

TABLE 1. Monoclonal Antibody Medications Currently Labeled for Pediatric Use by Indication

Indication ^a	Number of Medications
Hematology/oncology	11
Checkpoint inhibitors	6
Autoimmunity	9
Rare genetic conditions	7
Prevention of infection	6
Atopic disease	5
Prevention of transplant rejection	2

^aMedications with indications in multiple categories are included only once.

side effects that do occur are related to a specific drug. Because of this, familiarity with side effects an important consideration for physicians that prescribe monoclonal antibodies (Table 2).

The most commonly used monoclonal antibodies in children are those that directly antagonize aberrant functioning of the immune system. Monoclonal antibody treatments for allergic disorders are generally very well tolerated. By targeting common pathways in atopic disease, these therapies often have multiple indications. For example, dupilumab, which targets the interleukin-4 receptor alpha, inhibits the activity of interleukin-4 and interleukin-13, interrupting a wide range of allergic processes. Dupilumab has indications for asthma, chronic rhinosinusitis with nasal polypsis, eosinophilic esophagitis, atopic dermatitis, and prurigo nodularis. Omalizumab binds to the Fc portion of circulating IgE, thereby preventing its insertion into mast cells, basophils, and eosinophils. Omalizumab has indications for asthma, chronic urticaria, chronic rhinosinusitis with nasal polypsis, and food-induced anaphylaxis. As research progresses, the number of indications—as well as age range covered by those indications—is likely to increase.

Monoclonal antibodies that neutralize infectious agents may target key proteins for cell entry (such as the F protein of respiratory syncytial virus), or they may be directed at epitopes of toxins that neutralize toxicity. In contrast to monoclonal antibodies directed against human proteins, the ongoing evolution of infectious agents means that antibodies that are initially effective may become less effective over time. This was seen in the variable effectiveness of monoclonal antibody therapies for severe acute respiratory syndrome coronavirus 2. The ability to rapidly develop monoclonal antibodies to neutralize pathogens during infectious outbreaks, such as Ebola virus, is an important public health capacity because the polyclonal antibody therapies derived from convalescent serum have not generally been effective.

Monoclonal antibodies used in cancer therapies include treatments targeting entire groups of cells (eg, rituximab that eliminates both cancerous and noncancerous B cells). Monoclonal antibodies targeting specific oncogene products, such as human epidermal growth factor receptor 2, are more commonly used in adult patients. As with the evolution of pathogens, cancers also can evolve mechanisms to overcome the effectiveness of these treatments. Beyond targeting cancerous cells directly, an increasing number of checkpoint inhibitors have been developed. Immune checkpoints block immune responses; when appropriately invoked, immune checkpoints prevent immune activation against targets that are benign. However, the immune checkpoints also inhibit immune attacks against cancerous cells. Medications that inhibit checkpoints allow the immune system to attack cancerous cells.

Most of the conventional medications used in treating autoimmune disorders have large effects on autoimmune T cells but relatively modest effects on autoreactive B cells. Monoclonal antibodies used to deplete B cells and other components of inflammation provide superior outcomes in comparison with traditional medications. However, these immunosuppressive therapies increase the risk of opportunistic infection; careful evaluation is needed before and during treatment. Immunologists increasingly comanage patients with severe autoimmune diseases who experience life-threatening infections while on therapy.

Less commonly used monoclonal antibodies target proteins in specific medical conditions. For example, alirocuma targets the proprotein convertase subtilisin/kexin type 9 enzyme for patients with high cholesterol associated with heterozygous familial hypercholesterolemia, and pozelimab is used to treat CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy. The investment in research for developing medications for rare disorders, when spread among the lower number of patients who would benefit from it, can lead to prohibitive costs. There are substantial incentives for drug development for such “orphan diseases” that have been somewhat successful in prompting research on monoclonal antibody treatments.

Challenges in using monoclonal antibody therapies include cost, difficulty in obtaining prior insurance coverage authorization, the need to partner with specialty pharmacies, and the many other barriers accessing health care that limit access of patients to physicians comfortable with their use. These medications are generally not thought to be disease modifying, and many patients are uncomfortable with the prospect of lifelong treatment. This is especially true because most monoclonal antibody therapies are administered

TABLE 2. Monoclonal Antibodies With FDA-Approved Induction in Children

Name	Target	Indication	Hematology/Oncology	Indicated Age	Common Adverse Reactions
Blinatumomab	CD19, CD3; murine bispecific tandem scFv	B-cell precursor ALL including relapsed and refractory disease	All ages		CRS, infusion reactions, neurological toxicity (including immune effector cell-associated neurotoxicity syndrome), infection, pancreatitis, TLS, neutropenia and febrile neutropenia, elevated liver enzymes, leukoencephalopathy, benzyl alcohol toxicity in neonates, and embryo-fetal toxicity
Brentuximab vedotin	CD30; chimeric IgG1, ADC	CHL <i>Previously untreated high-risk CHL in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide</i>	≥2 y of age		Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, mucositis, thrombocytopenia, and febrile neutropenia
Denosumab	RANK-L; human IgG2	Giant cell tumor of bone <i>Unresectable or where resection would result in significant morbidity</i>	Skeletally mature adolescents		Hypocalcemia, impaired long bone growth, and inhibition of the eruption of dentition
Dinutuximab	GD2; chimeric IgG1	Neuroblastoma	All ages with high risk of developing		Pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased ALT, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased AST, and hypocalcemia, infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome
Eculizumab	C5; humanized IgG2/4	aHUS	≥2 mo of age		Headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, and pyrexia
Enapalumab	IFN γ ; human IgG1	Primary HLH with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy	From birth		Infections, hypertension, infusion-related reactions, and pyrexia
Emicizumab	Factor IXa, X; humanized IgG4, bispecific	Hemophilia A	≥1 y of age		Headache, diarrhea, rash, nausea, dizziness, and urticaria
Gemtuzumab/ozogamicin	CD33; humanized IgG4, ADC	Newly diagnosed CD33-positive AML; relapsed or refractory CD33-positive AML	≥1 mo of age with newly diagnosed CD33-positive AML; ≥2 y of age with relapsed or refractory CD33-positive AML		Hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis
Inotuzumab/ozogamicin	CD22; humanized IgG4, ADC	Relapsed or refractory CD22-positive B-cell precursor ALL	≥1 y of age		Thrombocytopenia, pyrexia, neutropenia, infection, anemia, vomiting, leukopenia, hemorrhage, fatigue, nausea, febrile neutropenia, headache, transaminases increased, abdominal pain, and γ -glutamyltransferase increased, and hyperbilirubinemia
Naxitamab	GD2; humanized IgG1	Relapsed or refractory high-risk neuroblastoma in the bone or bone marrow <i>Who have demonstrated a partial response, minor response or stable disease following prior therapy</i>	≥1 y of age		Infusion-related reaction, pain, tachycardia, vomiting, cough, nausea, diarrhea, decreased appetite, hypertension, fatigue, erythema multiforme, peripheral neuropathy, urticaria, pyrexia, headache, injection-site reaction, edema, anxiety, localized edema, and irritability
Tocilizumab	IL-6R; humanized IgG1	CAR T cell-induced severe or life-threatening CRS	≥2 y of age		Upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection-site reactions

Continued

TABLE 2. Monoclonal Antibodies With FDA-Approved Induction in Children (Continued)

Name	Target	Indication	Indicated Age	Common Adverse Reactions
			Checkpoint Inhibitors	
Atezolizumab	PD-L1; humanized IgG1	Unresectable or metastatic ASPS	≥2 y of age	Fatigue/asthenia, decreased appetite, nausea, cough, and dyspnea
Avelumab	PD-L1; human IgG1	Metastatic Merkel cell carcinoma	≥12 y of age	Fatigue, musculoskeletal pain, infusion-related reaction, rash, nausea, constipation, cough, and diarrhea
Ipilimumab	CTLA-4; human IgG1	MSI-H or dMMR metastatic colorectal cancer <i>That has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan in combination with nivolumab</i>	≥12 y of age	Fatigue, diarrhea, pruritus, rash, colitis, nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia
Nivolumab	PD1; human IgG4	Metastatic melanoma	≥12 y of age	Fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, vomiting, and urinary tract infection
Pembrolizumab	PD1; humanized IgG4	Melanoma, cHL, PMBCL, TMB-H cancer	Adjuvant treatment of pediatric (≥12 y of age) patients with stage IIB, IIC, or III melanoma following complete resection; pediatric patients with refractory cHL or cHL that has relapsed after ≥2 lines of therapy; pediatric patients with refractory PMBCL or who have relapsed after ≥2 prior lines of therapy; pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options; pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma; pediatric patients with unresectable or metastatic TMB-H (≥10 mut/Mb) solid tumors, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options	Fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism
Relatlimab	LAG-3; human IgG4	Unresectable or metastatic melanoma	≥12 y of age	Musculoskeletal pain, fatigue, rash, pruritus, and diarrhea

Continued

TABLE 2. Monoclonal Antibodies With FDA-Approved Induction in Children (Continued)

Name	Target	Indication	Indicated Age	Common Adverse Reactions
Autoimmunity				
Adalimumab	TNF α	JIA, Crohn disease, UC, hidradenitis suppurativa, noninfectious uveitis	≥ 2 y of age with JIA; ≥ 6 y of age with moderate to severe Crohn disease; ≥ 5 y of age with moderate to severe UC; ≥ 12 y of age with hidradenitis suppurativa; ≥ 2 y of age with noninfectious intermediate, posterior and panuveitis	Infections (eg, upper respiratory, sinusitis), injection-site reactions, headache, and rash
Belimumab	BlyS; human IgG1	SLE and lupus nephritis	≥ 5 y of age	Nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis
Canakinumab	IL-1 β ; human IgG1	Periodic fever syndromes (CAPS, TRAPS, HIDS/MKD, FMF) and Still disease (SJIA)	≥ 4 y of age with CAPS; all ages with TRAPS, HIDS/MKD, and FMF; ≥ 2 y of age with SJIA	CAPS: nasopharyngitis, diarrhea, influenza, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, weight increase, musculoskeletal pain, and vertigo; TRAPS, HIDS/MKD, and FMF: injection-site reactions and nasopharyngitis; SJIA: infections (nasopharyngitis and upper respiratory tract infections), abdominal pain, and injection-site reactions
Infliximab	TNF; chimeric IgG1	Crohn disease and UC <i>With reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy</i>	≥ 6 y of age	Infections (eg, upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain
Ixekizumab	IL-17a; humanized IgG4	Plaque psoriasis (moderate to severe disease)	≥ 6 y of age	Infections; hypersensitivity reactions, and inflammatory bowel disease
Ravulizumab (ravulizumab-cwvz)	C5; humanized IgG2/4	PNH and aHUS	≥ 1 mo of age with PNH; ≥ 1 mo of age with aHUS	PNH: upper respiratory tract infection and headache, injection-site reactions, and diarrhea; aHUS: upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension, and pyrexia
Rituximab	CD20; chimeric IgG1	Mature B-cell NHL/B-AL (with previously untreated, advanced-stage, CD20-positive DLBCL, BL, CLL, or mature B-AL in combination with chemotherapy); GPA (Wegener's granulomatosis) and MPA	≥ 6 mo of age with mature B-cell NHL/B-AL; ≥ 2 y of age with GPA and MPA	Mature B-cell NHL/B-AL: febrile neutropenia, stomatitis, enteritis, sepsis, ALT increase, and hypokalemia; GPA and MPA: infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, and infusion-related reactions
Secukinumab	IL-17a; human IgG1	Active ERA, plaque psoriasis (moderate to severe), active psoriatic arthritis	≥ 4 y of age with active ERA; ≥ 6 y of age who are candidates for systemic therapy or phototherapy for plaque psoriasis; ≥ 2 y of age who weigh ≥ 15 kg for psoriatic arthritis	Nasopharyngitis, diarrhea, and upper respiratory tract infection
Ustekinumab	IL-12/23; human IgG1	Psoriasis (moderate to severe), psoriatic arthritis	≥ 6 y of age	Nasopharyngitis, upper respiratory tract infection, headache, and fatigue

Continued

TABLE 2. Monoclonal Antibodies With FDA-Approved Induction in Children (Continued)

Name	Target	Indication	Prevention of Infection	Indicated Age	Common Adverse Reactions
Ansuvimab-zykl	Ebola virus; human IgG1	Ebola virus infection	From birth		Pyrexia, tachycardia, diarrhea, vomiting, hypotension, tachypnea, and chills
Atoltivimab, mafivimab, and odesivimab-ebgn	Ebola virus; mixture of 3 human IgG1	Ebola virus infection	From birth		Pyrexia, chills, tachycardia, tachypnea, and vomiting
Nirsevimab	F1 and F2 subunits of RSV fusion protein	RSV prevention	All infants up to 8 mo of age, born during—or entering—their first RSV season, and for a small group during their second season if they are between 8 and 19 mo old and at high risk for severe disease (including children who are severely immunocompromised)		Rashes and irritation at injection site, possible anaphylaxis, and caution in children with bleeding disorders
Obiltoximab	PA of <i>Bacillus anthracis</i> exotoxin; chimeric IgG1	Inhalational anthrax due to <i>B. anthracis</i> <i>In combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate</i>	Safety not tested in pediatric populations; solely based on adult and animal studies; population PK approach and weight-based dosing for children; pediatric patients: >40 kg: 16 mg/kg, > 15–40 kg: 24 mg/kg, ≤15 kg: 32 mg/kg		In adults (assumed similar to pediatric population): headache, pruritus, infections of the upper respiratory tract, cough, vessel puncture-site bruise, infusion-site swelling, nasal congestion, infusion-site pain, urticaria, and pain in extremity
Palivizumab	RSV; humanized IgG1	Prevention of serious lower respiratory tract disease caused by RSV	≤6 mo of age at the beginning of RSV season with a history of premature birth (≤35 wk gestational age) OR BPD that required medical treatment within the previous 6 mo and who are ≤24 mo of age at the beginning of RSV season OR hemodynamically significant CHD and who are ≤24 mo of age at the beginning of RSV season		Anaphylaxis and anaphylactic shock (including fatal cases) and other severe acute hypersensitivity reactions
Raxibacumab	<i>B. anthracis</i> PA; human IgG1	Inhalational anthrax due to <i>B. anthracis</i> <i>In combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate</i>	Safety not tested in pediatric populations; solely based on adult and animal studies; population PK approach and weight-based dosing for children		Rash, pain in extremity, pruritus, and somnolence

Continued

TABLE 2. Monoclonal Antibodies With FDA-Approved Induction in Children (Continued)

Name	Target	Indication	Rare Genetic Conditions	Indicated Age	Common Adverse Reactions
Alirocumab	PCSK9; human IgG1	High cholesterol associated with heterozygous familial hypercholesterolemia <i>Adjunct to diet and other LDL-C-lowering therapies</i>	≥8 y of age		Hypersensitivity reactions
Burosumab (burosumab-twza)	FGF23; human IgG1	XLH and FGF23-related hypophosphatemia in TIO associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized	≥6 mo of age with XLH; ≥2 y of age with TIO		XLH: pyrexia, injection-site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, and dental caries; TIO: tooth abscess, muscle spasms, dizziness, constipation, injection site reaction, rash, and headache
Evinacumab	Angiotensin-like 3; human IgG4	HoFH	≥5 y of age		Nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, nausea, and fatigue
Evolocumab	PCSK9; human IgG2	High cholesterol associated with heterozygous and HoFH	≥10 y of age		Nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. If established cardiovascular disease: diabetes mellitus, nasopharyngitis, and upper respiratory tract infection
Lanadelumab	Plasma kallikrein; human IgG1	Prophylaxis to prevent attacks of HAE	≥2 y of age		Injection-site reactions, upper respiratory infections, headache, rash, dizziness, diarrhea, and myalgia
Pozelimab	Complement 5; human IgG4	CD55-deficient PLE, also known as CHAPLE disease	≥1 y of age		Upper respiratory tract infection, fracture, urticaria, and alopecia
Teplizumab	CD3; humanized IgG1	Delaying the onset of stage 3 type 1 diabetes with stage 2 type 1 diabetes	≥8 y of age		Lymphopenia, rash, leukopenia, and headache
Atopic Disease					
Benralizumab	IL-5Rα; humanized IgG1	Severe eosinophilic asthma <i>Used with other asthma medicines for the maintenance treatment of asthma patients whose asthma is not controlled with their current asthma medicines</i>	≥12 y of age		Headache and pharyngitis
Dupilumab	IL-4Rα; human IgG4	AD (moderate to severe disease not adequately controlled with topical prescription or when those therapies are not advised), asthma (moderate to severe, characterized by eosinophilic phenotype or with oral corticosteroid-dependent asthma), eosinophilic esophagitis	≥6 mo of age with AD; ≥6 y of age with asthma; ≥1 y of age weighing ≥15 kg with eosinophilic esophagitis		AD: injection-site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, dry eye, and eosinophilia; asthma: injection-site reactions, oropharyngeal pain, and eosinophilia; eosinophilic esophagitis: injection-site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections

Continued

TABLE 2. Monoclonal Antibodies With FDA-Approved Induction in Children (Continued)

Name	Target	Indication	Indicated Age	Common Adverse Reactions
Mepolizumab	IL-5; humanized IgG1	Severe asthma (eosinophilic phenotype) and hypereosinophilic syndrome	≥6 y of age with severe asthma; ≥12 y of age with hypereosinophilic syndrome	Headache, injection-site reaction, back pain, and fatigue
Omalizumab	IgE; humanized IgG1	Asthma (moderate to severe persistent with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids), IgE-mediated food allergy (reduction of allergic reactions [type I], including anaphylaxis, that may occur with accidental exposure to ≥1 foods. To be used in conjunction with food allergen avoidance) and CSU (who remain symptomatic despite H1 antihistamine treatment)	≥6 y of age with asthma; ≥1 y of age with IgE-mediated food allergy; ≥12 y of age with CSU	Asthma: nasopharyngitis, headache, pyrexia, upper abdominal pain, pharyngitis streptococcal, otitis media, viral gastroenteritis, arthropod bites, and epistaxis; IgE-mediated food allergy: injection-site reactions and pyrexia; CSU: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough
Tezepelumab	Thymic stromal lymphopoietin; human IgG2	Asthma (severe)	≥12 y of age	Pharyngitis, arthralgia, back pain, and hypersensitivity reactions
Prevention of Transplant Rejection				
Basiliximab	IL-2R; chimeric IgG1	Prevention of organ (kidney, liver) transplant rejection	≥1 y of age	Urinary tract infection, hypertrichosis, rhinitis, pyrexia, hypertension, upper respiratory tract infection and viral infection, sepsis, and constipation
Muromonab-CD3	CD3; murine IgG2a	Reversal of organ (kidney, liver) transplant rejection	≤12 y of age	Diarrhea, nausea, vomiting, fevers, chills, muscle or joint pain, headache, infections, and thrombocytopenia

Abbreviations: AD, atopic dermatitis; ADC, antibody-drug conjugate; aHUS, atypical hemolytic uremic syndrome; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AML, acute myeloid leukemia; APS, alveolar soft part sarcoma; AST, aspartate transaminase; B-AL, B-cell acute leukemia; BL, Burkitt lymphoma; BLS, B-lymphocyte Stimulator; BPD, bronchopulmonary dysplasia; CAPS, cryopyrin-associated periodic syndromes; CAR, chimeric antigen receptor; CD, cluster of differentiation; CHAPLE, hyperactivation of complement, angioathic thrombosis, and protein-losing enteropathy; CHD, congenital heart disease; cHL, classical Hodgkin lymphoma; CRS, cytokine release syndrome; CSU, chronic spontaneous urticaria; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; DLBCL, diffuse large B-cell lymphoma; dMMR, mismatch repair deficient; ERA, enuresis-related arthritis; FDA, Food and Drug Administration; FGF23, fibroblast growth factor 23; FMF, familial Mediterranean fever; GPA, granulomatosis with polyangiitis; HAE, hereditary angioedema; HIDS, hyperimmunoglobulin D syndrome; HLH, hemophagocytic lymphohistiocytosis; HoFH, homozygous familial hypercholesterolemia; IFN, interferon; Ig, immunoglobulin; IL, interleukin; JIA, juvenile idiopathic arthritis; LAG-3, lymphocyte activation gene-3; LDL-C, low-density lipoprotein cholesterol; MKD, mevalonate kinase deficiency; MPA, microscopic polyangiitis; MSI-H, microsatellite instability-high; mut/Mb, mutations/megabase; PA, protective antigen; PD-L1, programmed death-ligand 1; PK, pharmacokinetic; PLE, protein-losing enteropathy; PMBCL, primary mediastinal large B-cell lymphoma; PNH, paroxysmal nocturnal hemoglobinuria; PCSK9, proprotein convertase subtilisin/kexin type 9; RSV, respiratory syncytial virus; scFv, single-chain variable fragment; SIIA, systemic JIA; SLE, systemic lupus erythematosus; TIO, tumor-induced osteomalacia; TLS, tumor lysis syndrome; TMB-H, tumor mutational burden-high; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; UC, ulcerative colitis; XLH, X-linked hypophosphatemia.

through subcutaneous injections. Patients with public insurance and those identified as racial or ethnic minorities are less likely to be prescribed monoclonal antibodies for asthma management. This differential prescribing is likely also present for the less-common conditions for which monoclonal antibodies are being prescribed. There is a need for monitoring equitable use of these medications in populations that experience the greatest need.

The small number of children with rare conditions makes trials with patients in the pediatric age range less attractive to companies weighing the cost of conducting studies with the potential return on that investment. Without explicit FDA approval for medications in a younger age group, insurance companies routinely deny coverage. A pediatric gastroenterologist in Louisiana successfully advocated for state law ensuring insurance coverage of medications lacking a label for children. This demonstrates that state-level advocacy is effective in gaining access to these medications for children.

As the safety of using monoclonal antibodies has become clear, they are increasingly dispensed to patients for home use. Families gain comfort with using prefilled syringes and autoinjectors over time. When paired with telehealth visits to the subspecialists who prescribe these medications, the ability to dispense medications to families for home use holds promise for increasing access to this class of medication.

Comment: I still vividly recall the first patient I witnessed being started on a monoclonal antibody for Crohn's disease. I was a pediatric resident on a gastroenterology rotation, and the 15-year-old boy before me was thin and morose, his

mother anxious and hyper-vigilant. The change after the boy's first infliximab infusion was dramatic. When he and his mother came for follow-up, they raved about the almost complete elimination of all his symptoms; a weight was lifted off their shoulders. And yet, while modern medicine is amazing, it is rarely purely miraculous.

Later during the rotation, I witnessed the utter disappointment of a family whose child was experiencing the lupus-like syndrome of joint pain, fatigue, and fever that can be associated with infliximab toxicity.

With the recent FDA approval of nirsevimab to protect infants against RSV, I am excited again for the miracle-like possibilities of a monoclonal antibody. The safety profile of nirsevimab is highly reassuring, so nirsevimab has been recommended for all infants up to 8 months old in their first RSV season, as well as some high-risk infants 8–19 months old in their second RSV season.

The first year after nirsevimab approval was plagued by drug shortages and unequal uptake among children. As we gradually see higher, more even coverage among all children, I am eagerly awaiting a winter season in which infants gasping for air in the "tripod position" is a rarity, not the norm, in urgent cares, emergency departments, and inpatient units.

Linda Fu, MD, MS
Associate Editor, In Brief

ANSWER KEY FOR MARCH PEDIATRICS IN REVIEW

Headache Care:

1. E; 2. D; 3. E; 4. E; 5. C

Acute Otitis Media:

1. E; 2. A; 3. C; 4. A; 5. D

Update in the Diagnosis and Treatment of Tuberculosis in Children:

1. D; 2. C; 3. D; 4. B; 5. D



10 Going on 2: A Case of Short Stature in an Immigrant Child

Laura Lewis, MD, MS,^{1,2} Priyanka Bakhtiani, MD¹

¹Children's Hospital Los Angeles, Los Angeles, California

²Keck School of Medicine of the University of Southern California, Los Angeles, California

PRESENTATION

An 11-year-old girl who recently moved to the United States from Guatemala presents with mild rhinorrhea. Per history, the child is healthy and has no medical issues except for difficulties with learning. However, per the mother's report, she has never seen a doctor before today, either in Guatemala or in the United States. No health evaluation of the child was done when the child moved to the United States from Guatemala, and any documentation of immunization or newborn screen is unknown.

The child was born at full term via cesarean section for breech presentation, with no prenatal or postnatal complications. However, her mother did not receive prenatal care before delivery. Her birth weight was 3.74 kg. During early childhood, her diet remained limited to canned foods and tortillas due to a lack of financial resources.

On physical examination, her vital signs are within normal ranges for age. Her height is 80 cm, which is 9.5 SDs below the mean for her age. Her height age is 2 years old. Her weight is 13.5 kg, which is 6.9 SDs below the mean. As a result, her body mass index is in the overweight category at the 92nd percentile, which is inconsistent with her history of poor appetite and insufficient caloric intake. The child has no clinical evidence of puberty. She is in a stroller meant for a toddler and is nonambulatory. She has coarse facies, a hoarse cry, an enlarged tongue, thick skin, and a protruding abdomen with a small reducible umbilical hernia. She does not have hepatosplenomegaly and has no apparent bony deformities (Figure 1). When asked, her mother mentions that the child's paternal aunt looks like her. Her speech and development are consistent with that of a 2-year-old child.

Given her short stature, coarse facies, and umbilical hernia, both mucopolysaccharidosis (MPS) and hypothyroidism are suspected. Thyroid-stimulating hormone (TSH) and free thyroxine (T4) are sent for laboratory results, and referrals are placed for medical genetics and endocrinology concurrently. Medical genetics is notably impressed by the clinical presentation and prioritizes the patient for an urgent evaluation, which includes urine testing for MPS disorders. Endocrinology provides preliminary recommendations while awaiting an appointment.

Abdominal ultrasound is unremarkable. Skeletal radiographs reveal normal cervical spine, scoliosis to 15 degrees, widening of the femoral necks bilaterally, and mild widening of the long bones of the bilateral lower extremities. Her echocardiogram is normal. She has an estimated skeletal age of 4 years based on

AUTHOR DISCLOSURES: Drs Lewis and Bakhtiani 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. A 10-year-old girl who is the height of a small 2-year-old girl. She is also noted to have macroglossia, a protuberant abdomen, a small umbilical hernia, poor tone, mild periorbital edema, and nonpitting pedal edema.

Greulich and Pyle's reference standards.¹ Serum chemistry is nondiagnostic; she has only a mild elevation in liver enzymes. Other tests are pending to confirm the diagnosis.

Due to viral symptoms on day of presentation, family declines catch-up vaccines. However, on subsequent visits, she is completely caught up on her immunizations.

DIAGNOSIS

Testing for urinary mucopolysaccharides is positive, but subsequent confirmatory genetic tests, including the Invitae Mucopolysaccharidoses Plus Panel,² are negative. Significant elevation of the TSH to 708 uIU/mL, along with a low free T₄ level (<0.4 ng/dL, FT₄), confirms a diagnosis of severe primary (likely congenital) hypothyroidism. A thyroid ultrasound is performed to determine the etiology of hypothyroidism, which shows small and heterogeneous lobes without goiter.

DISCUSSION

Unrecognized and untreated hypothyroidism within the first 2 to 3 years of life leads to severe short stature and intellectual disability (Figures 2 and 3). Thyroid hormone (TH) is paramount for normal brain development and bone growth, especially in the first few years of life. Prompt diagnosis and management, thanks to universal newborn screening (NBS) in the developed world, has almost eradicated the profound detrimental effects of TH deficiency on growth and neurodevelopmental outcomes (cretinism). However, unrecognized congenital hypothyroidism (CH) continues to be a leading cause of preventable intellectual disability globally.³ As many as 70% of infants worldwide are born in areas that do not have access to NBS.⁴ A small percentage of parents

within the United States continue to refuse NBS.⁵ Also, a delayed postnatal TSH surge, as commonly seen in premature infants, can result in a missed diagnosis if NBS is only collected within the first day or two of life.^{6,7} Thus, it is important for pediatricians to maintain familiarity with the clinical presentation of untreated CH.

The incidence of primary CH is between 1 in 3000 and 1 in 2000, with the most common cause in North America being sporadic failure of normal thyroid gland development (thyroid dysgenesis). Globally, severe maternal or infant iodine deficiency is the most frequently seen pathology.⁸ Our patient comes from Guatemala, where iodine intake has recently improved in the general population. However, with a severely nutrient-limited diet described by the patient's mother, iodine deficiency remains a culpable contributor. Given her clinical presentation with severe short stature and developmental delay, we suspect that the onset of hypothyroidism was either congenital or within the first 2 to 3 years of life. Because her paternal aunt has a similar history, genetic causes leading to dyshormonogenesis are also possible (2%–5% of CH cases).⁹ We did not pursue further genetic testing to screen for genetic etiologies of CH in our patient because it would not have led to a change in clinical management. Thyroid ultrasound was pursued and revealed a small, underdeveloped thyroid gland, which could potentially suggest thyroid dysgenesis, the most common etiology of CH.

The clinical signs and symptoms of hypothyroidism can be nonspecific and generalized due to the multifaceted role of TH in the body (Table 1). The role of TH in neurodevelopment and growth is illustrated by the significant short stature and global developmental delay noted in our patient. Low metabolism and increased systemic vascular

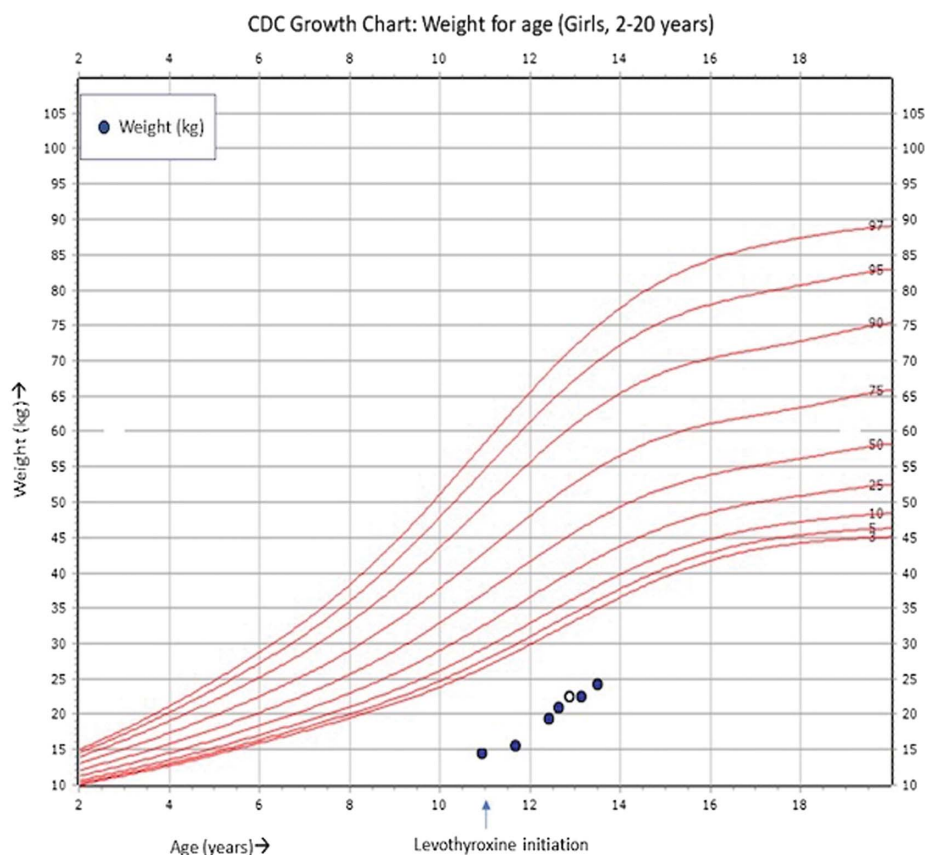


FIGURE 2. Centers for Disease Control and Prevention stature-for-age percentiles chart for girls aged 2 to 20 years reveals height at -9.5 SD for age.

resistance secondary to severe hypothyroidism can lead to bradycardia, hypothermia, myxedema, and increased weight gain despite poor appetite. Low muscle tone is responsible for the inability to bear weight, protuberant abdomen, umbilical hernia, and appearance of macroglossia. Constipation, coarse skin and hair, delayed dentition, poor feeding, and poor dentition were other characteristic symptoms elicited on further evaluation. Delayed bone development can result in wide-open fontanelles, delayed dentition, and delayed bone age. Direct hyperbilirubinemia due to the role of TH in maintaining bile flow is often noted in infants with untreated CH. The mild aspartate aminotransferase and alanine aminotransferase elevation seen in our patient can also be explained by myopathy caused by T_4 deficiency.¹⁰

TH also plays a crucial role in the onset of puberty, and untreated hypothyroidism can be associated with a delayed onset of puberty. Following this pattern, our patient presented aged 11 years with no clinical signs or biochemical evidence of puberty. However, there are cases in which hypothyroidism can actually lead to precocious puberty.

Van-Wyk-Grumbach syndrome is a reported clinical entity seen with severe primary hypothyroidism in which the significantly elevated level of TSH is speculated to directly stimulate the FSH receptor and lead to the early onset of puberty despite a delayed bone age.

In the presence of clinical suspicion, a significant TSH elevation with a low or normal FT_4 level can help establish the diagnosis of primary hypothyroidism. Once confirmed, treatment should be started with oral daily levothyroxine as soon as possible, regardless of the etiology of hypothyroidism. Treatment for CH should ideally be initiated within 2 weeks of age to achieve normal cognitive development. The initial starting dose of levothyroxine in infants is 10 to 15 $\mu\text{g/kg/d}$, whereas older children with primary hypothyroidism are usually started on 2 to 4 $\mu\text{g/kg/d}$. In comparison, adults are typically started on levothyroxine 1 to 2 $\mu\text{g/kg/d}$. Dosing is titrated over time to maintain TSH within a normal age-appropriate reference range. With profound hypothyroidism, as seen in our case, abrupt initiation of maximal dose replacement therapy can precipitate fatal arrhythmias, myocardial infarction events, or pseudotumor

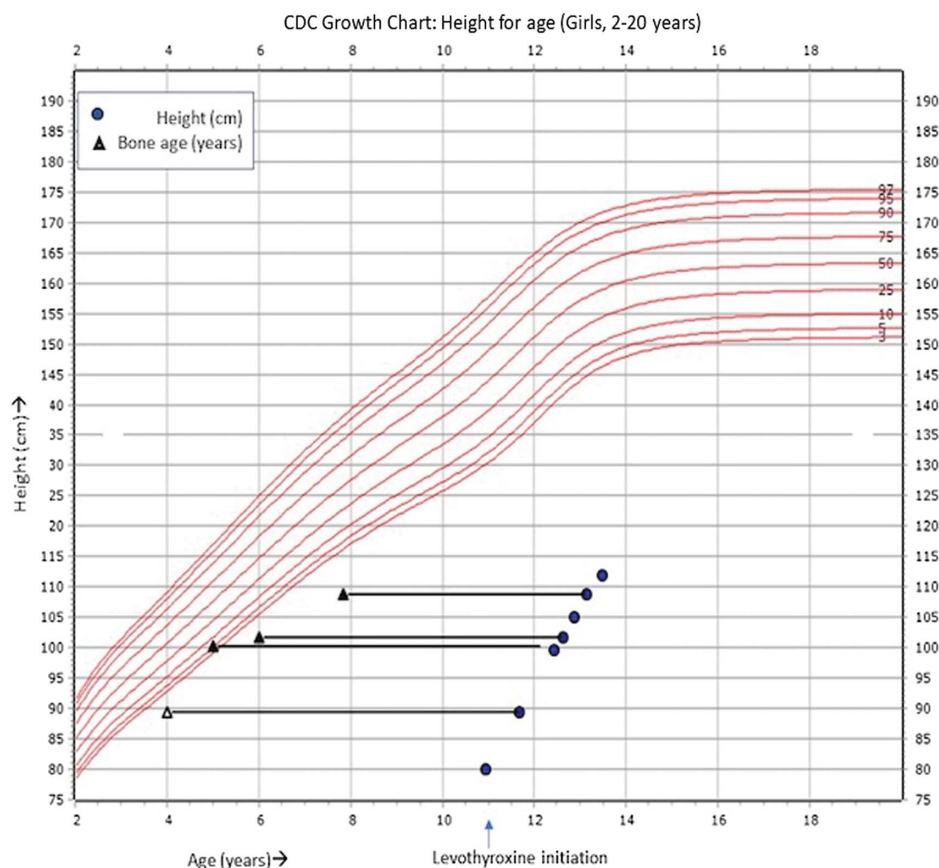


FIGURE 3. Center for Disease Control and Prevention weight-for-age percentiles chart for girls aged 2 to 20 years reveals weight at -6.9 SD for age.

cerebri.^{11,12} Therefore, the usual approach is to start with a lower dose of levothyroxine and gradually titrate to a euthyroid state.

Interestingly, an MPS disorder such as Hurler syndrome was first suspected upon visualization of the patient. Despite being a lysosomal storage disease with vastly different pathogenesis, Hurler syndrome can mimic untreated CH. Both untreated CH and Hurler syndrome present with

short stature and developmental delay. Both can also present with coarsening of or changes to facial features and umbilical hernias, as seen in our patient.¹³ Some features typical of Hurler syndrome not noted in our patient include corneal clouding, organomegaly, hirsutism, and cardiac abnormalities.¹⁴

PATIENT COURSE

Our patient is started on a levothyroxine dose of $1 \mu\text{g}/\text{kg}/\text{d}$ initially. The dose is gradually uptitrated to $3 \mu\text{g}/\text{kg}/\text{d}$. The family has some initial struggles with adherence to the dosing regimen, including language barrier, uncertainty with transportation for picking up the medication, issues navigating our health care system for refills, and remembering to take the medication every day. However, after several clinic visits and with patient education, the family is able to consistently administer the medication. Her thyroid function test results are now within age-based reference ranges on this dose. After a year on levothyroxine, we have noticed a drastic improvement in her clinical appearance, symptoms, growth, and neurodevelopmental state. She attained thelarche at a

TABLE 1. Presentation of Severe Hypothyroidism

Presentation of Severe Hypothyroidism

- Short stature
- Hypotonia
- Constipation
- Poor feeding
- Delayed fusion of fontanelles
- Dry, coarse skin
- Coarse facial features
- Myxedema
- Umbilical hernia
- Hoarse cry
- Abdominal distention
- Sleepiness

chronologic age of 12 years despite having a concurrent delayed bone age of 6 years.

Summary

- Clinical presentations may mimic one another, so it is important to maintain a broad differential diagnosis on initial evaluation.
- Untreated CH is rare in the United States but can still be seen.
- Maintain some level of suspicion when confronted with a child who is not meeting growth or developmental milestones, especially (but not just) in those who may not have had an appropriately drawn, US newborn screen.
- Globally, iodine insufficiency is the leading cause of CH, with genetic causes being much less common.
- When starting levothyroxine for profound longstanding hypothyroidism, start at a lower dose

and titrate up to the weight-based goal slowly to avoid potentially fatal arrhythmias and/or myocardial infarction events that can result from sudden exposure to a normal amount of TH.

Acknowledgments

We are grateful to the patient's family for allowing us to share her case with the readers of this vignette.

Suggested Readings

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