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AUTHORS

Cecilia C. Guthrie, MD, FAAP, FACEP, Associate Professor, Department of Pediatrics, Section of Pediatric Emergency Medicine, The Children's Hospital at OU Medical Center, Oklahoma City

Yashas Nathani, MD, Clinical Assistant Professor, Section of Pediatric Emergency Medicine, Department of Pediatrics, The Children's Hospital at OU Medical Center, Oklahoma City

PEER REVIEWER

Richard Massone, MD, Assistant Director, Our Lady of Lourdes Medical Center ER, Camden, NJ

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RELIAS MEDIA

Acute Treatment of Pediatric Migraine

Primary headaches, especially migraines, are a common problem for adults and children who present to the emergency department (ED). Migraine headaches have been challenging to diagnose, especially in the pediatric population. In addition, there is no consensus on treatment of pediatric migraines in the ED, with the approach to treatment largely extrapolated from adult literature.

Epidemiology

The prevalence of headaches ranges from 37% to 51% in school-age children and increases to 57% to 82% in adolescence.[1] The prevalence increases with age, with nearly 80% of adolescents reporting at least one significant headache by age 15 years. A common primary headache type is migraine. About 16% of the world's population suffers from migraine headaches.[2] The prevalence of migraine headaches in the pediatric population ranges from 7% to 23%.[3] The prevalence of migraine in children increases with age.[4] In a large-scale meta-analysis of more than 25,000 cases, Lewis et al described the incidence of migraines to be 2% at 3 to 7 years of age, 7% at 7 to 11 years of age, and 20% at 11 to 15 years of age.[5] The authors of a Finnish study conducted between 1974 and 2002 demonstrated an increase in prevalence of migraine from 14.5/1,000 to 91.9/1,000 for migraines with and without aura in children 7 years of age.[6] Similarly, over a two-year period, the authors of a Taiwanese study showed an increase from 5.2% to 7.4% in migraines in children 13 to 15 years of age.[7]

A chief complaint of headache is reported in approximately 0.6% to 1.3% of all visits to the pediatric ED.[8] Sheridan et al reported that approximately 40% of patients presenting to an ED with a complaint of headache were diagnosed with a primary headache disorder, and approximately three-fourths of these patients were diagnosed with a migraine.[9] It also is common for children to present to the ED, typically after the migraine has been ongoing for a couple of days, with one study reporting an average duration of 2.2 days of headache at the time of the ED visit.[10]

A gender predilection exists in which boys are affected by migraines more frequently before puberty, and females are predominant after puberty, with a ratio of adolescent females to males of 3:1.[11] However, the higher prevalence numbers for adolescents may be influenced by the higher likelihood of adolescents presenting to the ED for migraines compared to younger children. Lewis et al noted that 1% of the teenage population and approximately 3% of female teenagers may experience chronic migraines.[12]

Impact on Life (Morbidity)

Migraine is a leading cause of disability across all age groups. For adults, in addition to missed work days and the burden it causes to employers, the impact of migraines can extend to challenges at home when caring for their family members.[13]

EXECUTIVE SUMMARY

- The clinical criteria for pediatric migraines include an episodic headache with five or more attacks lasting two to 72 hours that cannot be explained better by medication overuse or another diagnosis.
- Typical migraine characteristics (such as pulsating quality, pain intensity, and impact on physical activity) and associated symptoms (such as vomiting, nausea, photophobia, and phonophobia) contribute to the diagnosis.
- The typical migraine patient has a non-focal normal neurologic exam.
- For patients with mild headache and tolerating oral fluids, initial treatment with oral hydration and ibuprofen is recommended; consider intranasal sumatriptan if > 12 years of age, early in the course, and not previously given within 24 hours.
- For patients with moderate to severe headache, begin intravenous (IV) hydration and start therapy with a combination of IV ketorolac and prochlorperazine, with or without adjunct diphenhydramine.
- If inadequate response after 60 minutes, consider IV magnesium sulfate or IV valproic acid.
- If inadequate response after an additional 60 minutes, consider contacting a pediatric neurologist for additional medication recommendations or admission for inpatient therapy.

In the pediatric population, disability includes missed school days and inability or decreased ability to participate in extracurricular and social activities. The 1989 National Health Interview Survey reported that out of 975,000 children, there were 164,454 school days missed.[14] Compared to their peers, children who experience migraine attacks often have poorer academic performance, difficulty paying attention while in class, and increased risk of other chronic conditions, such as depression and anxiety.[14]

The Pediatric Quality of Life Inventory v 4.0 (PedsQL 4.0) is a validated measure to assess quality of life in relation to chronic disease in children between 2 and 18 years of age.[15] It is a subjective self-evaluation of the child's functioning and emotional well-being. This questionnaire incorporates responses from children and parents and assesses four domains: emotional, social, school health, and physical health. Using the PedsQL 4.0, Powers et al compared pediatric patients with migraines to healthy children and found impaired quality of life in all areas of functioning in patients with migraine, with adolescents reporting more impairment in school functioning and young children reporting more impairment in social functioning.[16] They also found that children with migraines reported disability patterns similar to children with rheumatoid arthritis and cancer.[16] Comorbid conditions, such as anxiety and depressive disorders, are more common in children with migraines, and this trend continues in adults.[17]

Assessing the effect of migraine on patients is important, as the ultimate goal of therapy is to improve the patient's life. The Pediatric Migraine Disability Assessment (PedMIDAS), which is a modification of the Migraine Disability Assessment, was developed as a subjective assessment of the effect of migraine headaches on children and adolescents over a three-month period. Hershey et al found that PedMIDAS was useful for assessing treatment strategies, with improved scores with the use of prophylactic medication.[18] In the ED, assessing the effect of migraines on a patient's life is important to determine the possible need for prophylaxis, which can be a suggestion for further discussion with the primary care physician or specialist, and lifestyle recommendations that can decrease headache triggers.

Pathophysiology

The pathophysiology of migraines is multifactorial, but the exact mechanism of migraine headaches still is largely undefined. Several theories have been proposed over the years and continue to be developed; however, the genetic nature of migraines is clear. Many familial and twin studies have shown that migraine headaches have a high degree of inheritance, with 80% to 90% of first- and second-degree relatives reporting a history of migraines.[19] Although no gene or genetic defect has been identified clearly and consistently in migraines with or without aura, three genes have been implicated in familial hemiplegic migraines: P/Q calcium channel (CACNA1A), ATPase (ATP1A2), and sodium channel (SCN1A).[19]

Genetically, the brain of a migraineur may be more excitable and more vigilant compared to the brain of a person without migraines.[20] The inherited alteration of brain excitability may cause the brain to process sensory information differently, even between migraine attacks.[2]

The trigeminal neurovascular system has been found to contribute to the activation and progression of migraines. The trigeminal sensory afferents that innervate meninges and larger blood vessels in the central nervous system become activated, which in turn activates other pain centers and centers associated with meningeal inflammation.[9] Several imaging studies using functional magnetic resonance imaging (fMRI) have shown activation of the trigeminal ganglion in patients with migraines.[2] Pain pathways appear to be sensitized with repeated episodes of trigeminal activation and, thus, may contribute to chronic migraines.[21]

There also is increasing evidence that cortical spreading depression — a transient wave of depolarization of the cortex and the underlying mechanism of aura — is involved in the activation of trigeminal nociception and trigger headache mechanisms.[22] It remains unclear how this theory applies to patients who report migraines without aura, which includes the majority of patients with migraines.

Migraine also is thought to be associated with cranial vasodilation. The primary dysfunction may originate from brainstem centers that regulate pain sensation and vascular tone. Neuropeptides, such as 5-hydroxytryptamine (5-HT), and calcitonin gene-related peptide (CGRP) may be responsible for the vascular phenomena seen in migraine.[9] 5-HT, also known as serotonin, is an inhibitory neuropeptide that may prevent the vasodilatory cascade, while CGRP is a potent vasodilator within

Table 1. Pediatric Migraine Criteria[25]

Pediatric Migraine

At least five headaches meeting the following criteria:

- Untreated or unsuccessfully treated headache that lasts two to 72 hours
- Presence of two of the following headache characteristics:
  - Bilateral or unilateral location (usually frontotemporal)
  - Pulsating quality
  - Moderate to severe pain intensity
  - Aggravation by or causing patient to avoid routine physical activities
- During headache, at least one of the following symptoms:
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- Not better accounted for by another diagnosis according to the International Classification of Headache Disorders

Pediatric Migraine with Aura

At least two headaches meeting the following criteria:

- At least one of the following fully reversible aura symptoms: Visual, sensory, speech and/or language, motor, brainstem, or retinal
- Three or more of the following:
  - At least one aura symptom spreads gradually over five minutes
  - Two or more aura symptoms occur in succession
  - Each individual aura symptom lasts five to 60 minutes
  - At least one aura symptom is unilateral (aphasia is unilateral, dysarthria is not unilateral)
  - Aura accompanied by headache or followed by headache within 60 minutes
- Not better accounted for by another diagnosis according to the International Classification of Headache Disorders

the central nervous system and may be a key component in triggering migraine attacks. This may explain the efficacy of triptans and CGRP receptor antagonists in aborting migraine headaches.

Another factor that plays a role in migraine headaches is hormones. Fluctuations in estrogen levels have been implicated in the onset of migraine attacks, with estrogen withdrawal prior to menses being a known trigger.[23] Some women taking oral contraceptive medications may experience an increase in headache severity and frequency during placebo weeks with decreased estrogen levels. Similarly, women in the postpartum period may have more headaches due to low estrogen levels.

Diagnosis

Most commonly, the diagnosis of headaches is based on criteria established by the International Headache Society (IHS) International Classification of Headache Disorders.[24,25] This tool classifies headaches into primary, secondary, and those caused by other cranial neuropathies and headache syndromes. Over time, this tool has been refined, thus helping improve the sensitivity and specificity for diagnosing childhood headaches, especially migraines. (*See Table 1.*)

When evaluating a patient with headache, the provider should differentiate between a primary and secondary headache and determine if the headache is a sign of a life-threatening etiology. Secondary headaches are the most common type of headache (49%) and the most common etiology is infectious.[8] Although painful and significantly affecting the patient's life, primary headache disorders are not life-threatening. Headaches without abnormal neurological or physical examination findings rarely are due to underlying disease processes, such as increased intracranial pressure, central nervous system infection, or malignancy.[3]

To facilitate an accurate diagnosis, a thorough history and physical examination is required. Documenting headache characteristics, such as frequency, duration, location, severity, quality, and pattern of headache, as well as triggers, associated symptoms, and family and social history, is crucial in the diagnosis and management of the headache. Conducting a comprehensive review of systems, medication use (prescribed, over-the-counter, and illegal/controlled substances), recent events, and a thorough physical examination including a detailed neurological examination further will aid in distinguishing primary from secondary headaches.

It is important to note that routine brain computed tomography (CT) imaging or MRI is not indicated for a child who presents with recurrent headaches and has a normal physical and neurological examination. Neurologic findings are present in 85% of patients with brain tumors within eight weeks and nearly 100% within 24 weeks of illness onset.[26] However, neuroimaging should be considered in patients with the red flags described in Table 2.[1]

Traditionally, occipital pain has been considered a red flag for pediatric headaches. However, research indicates that occipital headaches are not associated with intracranial pathology more than headaches in other locations.[27] Ancillary testing, such as lumbar puncture, laboratory studies, and/or electroencephalogram (EEG), is not indicated routinely for patients with headache in the setting of normal physical and neurological examination.

Primary and Secondary Headaches

Primary headaches include migraine and its variants, tension-type headaches, and other trigeminal autonomic cephalalgias. Tension-type headaches present with pressing or tightening quality of a bilateral headache, with increased pericranial tenderness being the most common abnormal finding. These headaches may or may not be associated with nausea, phonophobia, or photophobia. Trigeminal autonomic cephalalgias usually are unilateral, are accompanied by cranial parasympathetic autonomic features (such as increased lacrimation, nasal congestion, and conjunctival injection), and generally are ipsilateral to the headache. Other forms of primary headaches include cough, exercise, thunderclap, cold stimulus, external pressure, stabbing, nummular, hypnic, sexual activity-associated, and new daily persistent headaches.[25] Secondary headaches range from new headaches to significant worsening of pre-existing headaches that are a result of underlying pathology of a systemic disease or trauma. Some etiologies

Table 2. Red Flags for Considering Neuroimaging for Headaches

Patient Characteristics

- Younger than 3 years of age
- Underlying medical conditions: sickle cell disease, immunodeficiency, malignancy, pregnancy, coagulopathy, congenital heart disease, recent head trauma, seizure disorder
- Neurocutaneous syndromes: ash-leaf spots, café-au-lait spots, petechial rash, port wine stain

Headache Characteristics

- Early-morning pattern or early-morning waking with headache, nausea, or vomiting
- Worsening headaches with straining
- Explosive new onset
- Occipital pain
- Progressive frequency and severity of the headache
- Associated changes in mood or mental status or deterioration in school performance

Signs/Symptoms

- Persistent vital sign changes, such as hypertension with bradycardia or fever
- Severe, persistent nausea and vomiting
- Lightheadedness, vertigo, or unsteadiness
- Perioral or extremity paresthesias or other localized weakness (may still represent aura for classic migraine)

include vascular disorders, malignancy, infection, psychiatric disorders, increased intracranial pressure, trauma to head and/or neck, or substance abuse or withdrawal, among others.

Criteria for Migraine and Its Variants

Migraines can occur with or without an aura. In children, migraine without aura is the most common type and is reported with approximately two-thirds of migraines.[1,28] The five phases of migraine are prodrome, aura, headache, resolution, and postdrome.[20] Not all patients experience all phases during each attack. The prodromal phase occurs in up to 80% of migraineurs and begins 24 hours prior to the headache.[20] Prodromal symptoms include yawning, fatigue, changes in appetite, increased energy, frequent urination, difficulty with memory and concentration, irritability, and hyper-/hypo-sexuality. Typical postdrome symptoms include cognitive difficulties, dizziness, fatigue, and concern for recurrence of headache, which may last 24 to 48 hours. Patients describe this phase as feeling like a "hangover" or having been "run over by a truck."[20]

The criteria for pediatric migraines include an episodic headache with five or more attacks lasting two to 72 hours that cannot be explained better by medication overuse or another diagnosis. The patient has a non-focal normal neurologic exam. Typical migraine headache characteristics (such as pulsating quality, pain intensity, and impact on physical activity) and associated symptoms (such as vomiting, nausea, photophobia, and phonophobia) contribute to the diagnosis.

Differences between adult and pediatric migraine characteristics have been identified. Migraines in children may have a bilateral or non-throbbing nature and may be shorter in duration compared to those in adults. In addition, children may not be able to communicate symptoms, such as quality or photophobia, so inference from their behavior may be used, such as going to a dark room to lie down. Headache duration in adults ranges from four to 72 hours compared to two to 72 hours in children.[24] During the transition from late adolescence to early adulthood, the location of the headache becomes unilateral.[25]

Migraine with aura has additional neurologic symptoms, which are described as typical, brainstem, hemiplegic, or retinal.[25] A typical aura includes visual (zigzag lines with relative scotomas), sensory (unilateral paresthesia often ipsilateral to the headache and involving the hand, face, leg, and/or trunk), and speech/language (aphasia) symptoms. Speech/language aura is the least common among the typical auras. Brainstem aura includes symptoms such as dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia (not attributable to sensory deficit), and decreased level of consciousness (Glasgow Coma Scale < 13). Hemiplegic aura involves fully reversible motor weakness lasting less than 72 hours. Retinal migraines include repeated attacks of monocular visual disturbance, including scintillations, scotomata, or blindness, associated with migraine headache. These symptoms are reversible and may occur before, during, or after the headache, and may last up to 60 minutes following the headache. Migraine with aura may be difficult to distinguish from a more serious neurologic event secondary to the accompanying transitory neurologic findings. Migraine with aura may be underdiagnosed in the younger population because of the difficulty obtaining effective and reliable communication about specific aura symptoms. (*See Table 1.*)

In addition to the classic forms of migraine with or without aura, patients may present to the ED with a migraine variant. An important aspect of a migraine is the recurrent episodic nature of the headache and the ability to distinguish it from a few symptomatic migraine-like attacks. The IHS designates a minimum number of attacks at five.[25] In the ED, patients may present with headaches that meet migraine criteria except for the number of previous episodes. These patients may be identified as having probable migraine without aura.[25] See Table 3 for migraine variant characteristics and classification.

Acute Migraine Treatment

For pediatric headaches and migraines, outpatient, nonprescription abortive therapies of ibuprofen or acetaminophen have been shown to be effective. Ibuprofen has been found to be the superior agent.[29,30,31] (*See Table 4.*) Patients may present to the ED for migraine treatment when the headache reaches a level of intolerability and/or the symptoms persist despite home therapy.[10,32] In two multicenter studies, children who presented to the ED with a probable migraine headache or migraine

Table 3. Migraine Variants[3]

Migraine Variant	Description	Symptoms/Characteristics
Migraine with brainstem aura (formerly known as basilar migraine)	• Migraine with aura symptoms originating from the brainstem • No retinal or motor symptoms	• Two or more of the following reversible symptoms: dysarthria, tinnitus, vertigo, hypacusis, diplopia, ataxia, and decreased consciousness
Chronic migraine	• Lasting > 90 days or very frequent migraine attacks that fulfill the criteria to the right	• Fifteen or more days of headache per month for three or more months • Five or more attacks fulfilling migraine or migraine with aura criteria • Eight or more days of headache per month for three months fulfilling migraine/migraine with aura criteria or perceived to be migraine at onset by patients and relieved by triptan or ergot derivative
Familial hemiplegic migraine	• Migraine with aura in patients with one or more first- or second-degree relatives with history of attacks fulfilling criteria for hemiplegic migraine • More common in children	• Motor weakness AND visual, sensory, and/or speech/language disturbances, all of which are fully reversible
Status migrainosus	• Debilitating migraine with or without aura that lasts 72 to 90 hours	• Disability caused by pain or other symptoms of migraine • Typical presentation of previous attacks, except for severity and duration
Cyclic vomiting syndrome	• Recurrent episodic attacks of severe nausea and vomiting that are self-limiting and have a predictable pattern • Patients are asymptomatic between episodes	• Nausea and/or vomiting lasting at least one hour and up to 10 days, with episodes occurring more than one week apart • Nausea and vomiting occurring more than four times per hour during the episodes
Abdominal migraine	• Five or more attacks of abdominal pain lasting two to 72 hours if untreated or unsuccessfully treated	• Pain is dull in quality and periumbilical, midline, or sometimes poorly located • Moderate to severe in intensity

by IHS criteria had symptoms for an average of two days.[10,32] About 60% of patients with migraines had received oral analgesics prior to ED presentation.[10,33]

Systematic reviews of medication trials for pediatric migraine treatments demonstrate the lack of controlled trials of acute treatments for pediatric migraine overall but especially in the ED.[31,34] A recent systematic review of acute treatment for pediatric migraines reported seven specific treatment studies performed in the ED.[35] Although multiple treatment modalities exist for migraine abortive therapy, the majority of the literature is based on the adult population.[33,36,37]

Retrospective chart reviews, cohort studies, and database reviews reveal that various treatments are used in treating pediatric migraines in the ED. A multicenter study of children's hospitals in Canada noted significant variability of treatment between ED sites.[10] Eapen et al noted differences in treatment and admission rates between a pediatric and community ED.[32] Sheridan et al described significant variability in the evaluation and treatment of pediatric headache in the ED.[9] Guidelines in the literature have suggested different first- and second-line treatments.[38-40] A retrospective chart review by the Pediatric Emergency Research Canada reported the use of different abortive treatments for pediatric migraines, including dopamine antagonists (specifically, metoclopramide, prochlorperazine, and chlorpromazine) with and without diphenhydramine, nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamines, steroids, benzodiazepines, and opioids.[10] Bachur et al also noted variability of treatment in a retrospective database study in 2015.[41]

Intravenous Fluid Hydration

Children with migraine may have symptoms of nausea and vomiting and, therefore, may have decreased oral intake with increased fluid losses. Treatment with intravenous (IV) fluids is variable and has been reported from 10% to 50%.[10] Published guidelines for treating pediatric migraines include IV fluid therapy.[39,40] Authors of a Canadian multicenter, retrospective review found that the use of IV fluid hydration in the treatment of pediatric migraine is common.[42] The authors of a randomized, controlled trial (RCT) found no decrease in pain with IV fluids when comparing the expectation of medicine and no medicine with the fluid after 30 minutes of therapy.[43] The use of IV fluids did not improve pain scores and was not associated with sustained headache relief up to 48 hours post-discharge from the ED.[44]

Table 4. Abortive Medications in the ED

Drug	Dosing	Side Effects	Contraindications
Prochlorperazine Metoclopramide	0.15 mg/kg (IV), max 10 mg 0.1 mg/kg (IV), max 10 mg	Extrapyramidal side effects, sedation, prolong QT	Bone marrow depression
Sumatriptan	5 to 20 mg (IN)		History of stroke, cardiovascular disease, uncontrolled hypertension, hemiplegia, migraine
Ibuprofen Ketorolac	10 mg/kg, max 800 mg 0.5 mg/kg (IV), max 30 mg	Gastrointestinal upset	
Diphenhydramine	1 mg/kg, max 50 mg	Sedation	Platelet disorders
Magnesium	25 to 50 mg/kg, max 2 g	Nausea, vomiting, hypotension, flushing	
Valproic acid	15 mg/kg, max 1 g	Nausea, dizziness, tachycardia, paresthesia	Pregnancy, hepatic disease, mitochondrial disorders, metabolic disorders

IV: intravenously, IN: intranasally

Since ED patients may receive IV medication therapy, providing fluid therapy may help rehydrate with little risk. In addition, fluid hydration may help provide renal protection with the use of IV nonsteroidal anti-inflammatory treatment, such as ketorolac.[45]

Dopamine Receptor Antagonist

The role of dopamine receptor antagonists (DRAs) for migraine has evolved over time. Initially, DRAs were used for treating the nausea and vomiting associated with migraines. With the development of the trigeminal cascade pathophysiology hypothesis for migraine, DRAs have a role in treatment overall. The DRAs used most commonly are prochlorperazine and metoclopramide.[41] Prochlorperazine is the most studied DRA treatment for migraine in children. Metoclopramide has been well studied in the adult population for treatment of migraine. A recent retrospective study comparing prochlorperazine, metoclopramide, and promethazine effectiveness in the ED was the first that specifically defined effectiveness for metoclopramide in pediatric migraine treatment.[46] Other less commonly used DRAs are chlorperazine and haldol.

The reported efficacy of prochlorperazine ranges from 75% to 86%.[47-51] Sheridan et al found that metoclopramide was less effective than prochlorperazine. Treatment failure occurred with metoclopramide, and the medication resulted in less than 50% pain reduction, odds ratios of 3.5 (95% confidence interval [CI], 0.6-20.22) and 3.2 (95% CI, 0.88-11.4), respectively, when compared to prochlorperazine.[46] Adult studies also have shown metoclopramide to be inferior to or no better in effectiveness than prochlorperazine.[52,53] Promethazine and chlorperazine are less effective in the treatment of pediatric migraines compared to prochlorperazine and metoclopramide (57% and 60%, respectively).[46,48] In addition, a large database study showed treatment with metoclopramide increased the odds for an ED revisit within three days compared to prochlorperazine.[41]

Side effects from DRAs include dystonia and akathisia. Diphenhydramine has been used as an adjunct medication to prevent extrapyramidal side effects. Vinson and Drotts reported a decrease in akathisia in adults when diphenhydramine was added to prochlorperazine for migraine treatment.[54] In 2016, Friedman et al reported no difference in efficacy or side effects in an RCT of adults using metoclopramide with or without diphenhydramine.[55]

Authors of retrospective studies involving acute migraine treatment with prochlorperazine in pediatric patients reported that the akathisia rate was 0% to 12%.[48,51] Brousseau et al reported akathisia in 3% of patients in an RCT involving prochlorperazine.[47] In other pediatric retrospective chart reviews with diphenhydramine given in addition to prochlorperazine, the akathisia rate was 0% to 6.5%.[40,49] Trottier et al specifically evaluated the rate of akathisia in a pediatric prospective cohort study that involved acute treatment with prochlorperazine and diphenhydramine in the ED. The Vinson scale for akathisia was used for evaluation of akathisia in the ED with telephone follow-up at 48 hours and seven days. Trottier et al observed a definite occurrence in 5%, with possible occurrence in an additional 34%.[50] In a study using the Pediatric Health Information System database, Bachur et al reported that 33% of patients treated for pediatric migraine received diphenhydramine. Treatment with diphenhydramine and DRA increased the odds of a return visit to the ED by 27% when compared to DRA treatment alone in pediatric patients.[41]

NSAIDs

NSAIDs have been shown to be successful for outpatient therapy of pediatric migraines. Ibuprofen is the most thoroughly investigated agent.[30,56] Ibuprofen was more effective for pain control than acetaminophen (odds ratio [OR], 2.2; 95% CI, 1.1-4.0) and placebo (OR, 2.9; 95% CI, 1-8.1) in pediatric migraineurs. Ketorolac is an IV NSAID commonly used as a treatment for migraine alone or in combination with other drugs in the ED. Studies have supported the efficacy of ketorolac.[57] Brousseau et al demonstrated an efficacy of 55% in pediatric migraines with ketorolac treatment alone.[47] In a 2014 RCT, 48% of patients treated with ketorolac did not need a second rescue medication in the ED.[58] Naproxen is another NSAID that is effective and commonly is used.[59,60]

Combination Therapy

When used as part of a hospital migraine treatment guideline, the combination therapy of a DRA and an NSAID with IV fluid administration was found to be more effective than monotherapy. In

a cohort study before and after guideline implementation with combination therapy, Leung et al found a significant decrease in the admission rate to 3% for migraine and a decrease in headache pain scores when combination therapy was given once, with admission if headache persisted.[39] Kaar et al also reviewed the hospital admission rate and pain score changes before and after implementation of a combination therapy guideline, which also incorporated a repeat dose of DRA as a second-line therapy and an antiepileptic drug as a third-line therapy prior to admission for treatment failure. They found that 12% of treated patients required a second dose of DRA and 39% of patients treated with the second dose were discharged home.[40]

In an RCT comparing prochlorperazine and ketorolac and then, if needed, crossing over the medications, the combination of both medications was most successful, with 93% effectiveness in discharging the patient home.[47] Another combination that has been investigated in the adult population is naproxen and sumatriptan. This combination has been demonstrated to be more efficacious than either agent alone.[61] Naproxen also has been studied in adolescents and was shown to have a favorable safety profile.[62]

Triptans

Triptans act on serotonin receptors (5-HT1B/1D), which have peripheral and central effects on neurovascular vasodilation.[20,63] Triptans have demonstrated efficacy in treating migraines in children and have been approved by the U.S. Food and Drug Administration for use in children and adolescents. Routes of delivery include oral agents, nasal sprays, and subcutaneous injection.[37] Intranasal sumatriptan is approved for adolescents in Europe.[33] The American Academy of Neurology recommends intranasal sumatriptan for acute migraine treatment because there are three studies with class I rating and it has a level A recommendation.[64] Triptans have not been studied in the ED for pediatric migraine treatment.

Studies show that the most effective time to give triptans for treatment of migraines is early in the course, while the headache is mild.[65] Upon presentation to the ED, the duration of the pediatric migraine is prolonged, with an average reported duration of approximately 48 hours, which may account for the uncommon use of triptans in ED treatment.[10,32,41]

Magnesium

Magnesium influences neurogenic inflammation that has been associated with migraine pathophysiology.[66] A meta-analysis of randomized, double-blind studies showed no beneficial effect at 30 minutes after magnesium treatment in adult migraneurs.[66] This result may have been influenced by the limitations of the studies, including inadequate power, the methodology of randomization, possible type II errors, and time constraint of 30 minutes.

In 2015, Shahrami et al found increasing efficacy in pain control with magnesium treatment of migraine at 20 minutes (35%), one hour (71%), and two hours (92%) post-treatment.[67] A pediatric case series of IV magnesium for acute treatment of headaches found minimal side effects and a response rate that was highest in patients with status migrainosus. Magnesium was given after multiple other medications had failed.[68]

Opioids

The American Academy of Neurology does not recommend opioids for primary headache treatment.[64] Opioid treatment may convert a migraine from an episodic to a chronic headache and potentiate pain with blunting of treatment response.[69] A retrospective database study and multisite chart review of pediatric EDs found that opioid use in the acute treatment of migraines ranges from 3% to 5%.[10,41] In a retrospective cohort study of state Medicaid claims and the Prescription Drug Monitoring Program, opioid prescribing rates after discharge from an ED or ambulatory care facility were identified. The ED prescribing rate was approximately 4%, which was higher than the ambulatory setting rate of 1%.

Dihydroergotamine

Dihydroergotamine (DHE) is an ergot alkaloid that acts as a 5-HT1 receptor antagonist and has been found to be effective in treating refractory migraines. Inpatient therapy typically requires multiple doses for resolution of the headache. Contraindications to DHE therapy include stroke, uncontrolled hypertension, pregnancy, and cardiovascular disease.

In a pediatric case series in which DHE was given for migraine without aura and status migrainosus, inpatient therapy had 74% to 80% effectiveness.[70,71] Patients initially were given dopamine receptor antagonists and then switched to ondansetron prior to the DHE doses to help relieve these symptoms. Initially, the patient may feel worse with side effects from the DHE, such as nausea, vomiting, transient increase in headache, and chest tightness.[70,71]

In a retrospective chart review, Nelson et al reported 63% of pediatric patients hospitalized for refractory headache responded to IV DHE. In addition, the headache resolved in 21% of all hospitalized patients and in 50% of patients diagnosed with status migrainosus.[72] In a small case series in which DHE therapy was given for refractory abdominal migraines, five of six patients had symptom resolution or significant improvement.[73] In a small outpatient study (n = 12) using a crossover design to compare oral DHE and placebo, researchers did not find a statistically significant improvement in pain.[74,75]

Peripheral Nerve Block

Inflammation of scalp nerves may contribute to headaches by conducting pain signals. Local anesthetic helps reduce pain by interrupting the nerve signal through inhibition of sodium channels.[76] There is no consensus on the specific local anesthetic, injection technique, or dose.[77] The local anesthetic may be used alone or in conjunction with corticosteroids.[75] Injection sites can be identified at points of maximal tenderness. Peripheral nerve blocks have been used in adults to treat a variety of headaches, including migraines.[77] In 2018, the authors of a systematic review and meta-analysis of seven RCTs found that greater occipital nerve (GON) blocks significantly decreased pain intensity and there was no increase in adverse events in adult migraineurs.[78]

GON blocks have been shown to have the greatest efficacy in children with chronic migraine and new daily persistent headache.[79,80] GON blocks also have improved pain in children with post-traumatic headache.[79,81] In a retrospective case series, Dubrovksy et al found good therapeutic effect in 93% of patients given a GON block and, occasionally, the lesser occipital nerve and supraorbital nerve, depending on the areas of scalp point tenderness.[79]

In a prospective RCT, adult migraine patients received GON block, placebo GON block, or IV dexketoprofen and metoclopramide. The authors reported that GON block was as effective as the IV medication and superior to the placebo GON block when the changes in median score were compared.[82] The median value change from baseline at 30 and 45 minutes after treatment showed a statistically significant difference when comparing the three arms. Limitations to the study include no blinding of the IV medication, the inability to generalize secondary to a single study site, a possible placebo effect with injections, and a small number of participants in the study (n = 60).

In a small (n = 28) randomized, sham-controlled trial of GON blocks in adults, researchers found some effectiveness (30% of participants achieved complete resolution of the headache) at 30 minutes post-treatment. Study participants were eligible if metoclopramide failure had occurred. The participants and outcome assessors were blinded. The study was stopped prior to achieving the projected sample size of 78 because of slow enrollment over 31 months.[83]

Valproic Acid

Valproic acid (VPA) is an antiepileptic medication used mainly as prophylaxis for migraine patients. It enhances gamma-aminobutyric acid neurotransmission and blocks the voltage-gated sodium channels and T-type calcium channels.[84] Although it has been used as prophylaxis for pediatric migraines, valproic acid was given as an acute migraine treatment in two small retrospective studies.[85,86] In a chart review, Reiter et al gave one dose of IV VPA at 1 g, and patients had a subsequent decrease in pain and were discharged home in 78% of visits. A second dose of 500 mg was given in 22% of visits.[85] In a case series of 13 patients, IV VPA was given as a second-line therapy, and 83% of the patients had pain improvement and were discharged home.[86] Although limitations included missing documentation and small numbers, the authors concluded that VPA may be helpful in the acute treatment of pediatric migraines.

In a recent retrospective study on the use of VPA in a continuous infusion after an initial bolus for inpatient therapy for pediatric status migrainosus, researchers reported VPA was well tolerated, and 64% of patients achieved 100% headache resolution by 48 hours from the start of infusion.[87]

Corticosteroids

The benefits of corticosteroid use in the treatment of acute migraine are uncertain. In a meta-analysis of RCTs in which patients received dexamethasone as adjunct treatment to standard abortive therapy, no benefit in pain reduction was seen; however, a reduction in headache recurrence was noted.[88] Conflicting results in other studies show no improvement in recurrence rates.[88,89] In a pediatric retrospective chart review, Cobb-Pitstick et al observed no significant decrease in migraine recurrence after acute treatment in the ED or inpatient therapy.[90]

Propofol

Propofol is an established medication used in procedural sedation in the ED. Studies using low-dose propofol in the acute treatment of migraine have been reported in adult and pediatric patients. In an adult case report[91] and pediatric case series,[92] low-dose propofol showed efficacy in pain control. In an RCT comparing the efficacy of propofol and subcutaneous sumatriptan, researchers found no difference in pain control at one and two hours after treatment.[93] Better antiemetic control was reported with the low-dose propofol.

Sheridan et al reported no significant difference in pain reduction in pediatric patients in an RCT comparing low-dose propofol (59%) and standard therapy (NSAID, DRA, and diphenhydramine; 51%).[94] Rebound headache was significantly more common in the standard therapy group (67%) compared to the low-dose propofol group (25%). Study limitations included no standardized low-dose propofol and the unblinded and underpowered nature of the study. Questions still remain regarding the effectiveness of propofol in the treatment of pediatric migraine, and further studies are needed.

Treatment Approach

See Figure 1 for an approach to treating children with possible migraine.

• Determine the severity of the patient's migraine and the patient's oral tolerance to liquids.

If the patient has a mild headache and is tolerating oral liquids, hydration with oral fluids and ibuprofen may resolve the headache. If nausea and vomiting are present, it may be more beneficial to treat with a DRA and IV hydration. Some published guidelines use ondansetron as the antiemetic.[1] A side effect of ondansetron is a headache, so it may be counterproductive. If the headache is mild and early in the course, sumatriptan may be given intranasally.

If the patient has a moderate or severe headache, begin IV hydration and start therapy with a combination of IV ketorolac and DRA, with or without adjunct diphenhydramine. Use prochlorperazine intravenously, as it is most efficacious. If prochlorperazine is unavailable, use metoclopramide.

• Reevaluate the status of the migraine 60 minutes after medications are given.

If the patient is not significantly better, consider magnesium sulfate or VPA as the next treatment. Check for pregnancy before giving VPA to female patients because it is contraindicated in pregnancy. Continue hydrating the patient, especially if giving magnesium sulfate.

• Reevaluate the status of the migraine 60 minutes after the second medication is given.

If the patient is not significantly better, administer the alternate option from the previous choice of magnesium sulfate or VPA. In addition, consider contacting a neurology specialist to aid in further medication decision-making.

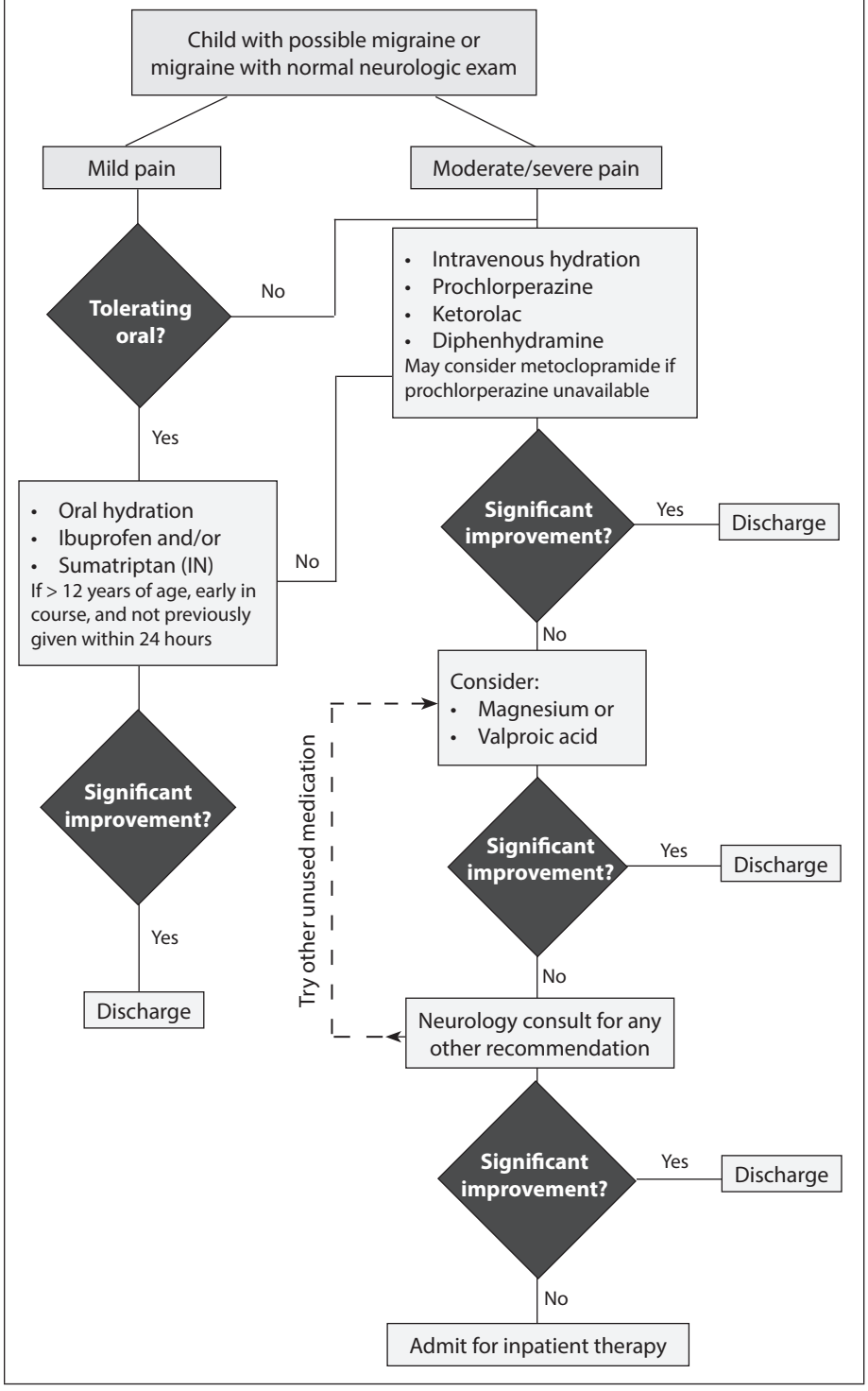
• Reevaluate the status of the migraine 60 minutes after the medication is given.

A neurology specialist may recommend other medications or admission for inpatient therapy.

• If the pain has resolved or decreased to a mild, tolerable level for the patient on reevaluation, discharge the patient home.

Discharge home with a prescription for naproxen, as medication overuse headache is less likely to occur than with ibuprofen or over-the-counter naproxen. Discuss limiting the number of days the NSAID is used to less than three times per week. Another option is to give a sumatriptan/naproxen combination (10/60 mg or 85/500 mg), which may be taken daily as needed for migraine. Have the patient keep a headache diary to help identify triggers of the migraine and to discuss it with the primary care provider or neurologist.

Figure 1. Approach to Treating Pediatric Migraine Patients



Common triggers for migraine attacks include changes in sleep-wake cycle, stress, dehydration, menstruation (due to fluctuating hormone levels), certain foods, and alcohol.[3] Migraine prophylaxis is recommended when headaches occur more than one day per week and significantly affect the patient's quality of life.[37]

Return ED Visits

After improvement of a migraine headache in the ED, some patients will experience a recurrence of migraine symptoms and will return to the ED. Headache recurrence and the return rate in different studies have different times of follow-up, from two to three days[47] to seven days[50] to one month.[95] The return rate in pediatric patients has been reported to range from 3% to 5%[48] to 11% to 12%.[47,50,95] Prescriptions for naproxen and corticosteroids have been given prior to discharge to decrease headache recurrence, with studies showing conflicting success. Analgesic overuse after discharge may contribute to recurrence. In a retrospective review using the hospital's ED database, Legault et al reported that acute treatment and discharge medicine did not influence the return rate.[95] Further study of this problem is needed.

Conclusion

Pediatric migraine is a common presentation to the ED and has a significant effect on quality of life. Acute treatment in the ED is variable, with a large amount of treatment based on the adult literature. Although the headache may resolve with treatment, the headache may recur within days to weeks, which contributes to patients returning to the ED. Further investigation into acute ED treatment and headache recurrence is warranted.

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1. Which of the following neuropeptides has been strongly implicated in the pathophysiology of migraines?
   a. Cocaine-and-amphetamine-regulated transcript
   b. Agouti-related peptide
   c. Calcitonin-gene-related-peptide
   d. Glucagon-like peptide-1
2. Low levels of which hormone are known to trigger migraines?
   a. Testosterone
   b. Progesterone
   c. Thyroxin
   d. Estrogen
3. A 12-year-old female presents with a chief complaint of headache. Which history would you consider concerning and order neuroimaging?
   a. History of asthma
   b. Recurrent mild headache which has not changed in frequency or severity
   c. Throbbing unilateral headache with normal physical examination
   d. Headache that wakes the patient from sleep in the early morning
4. What is the average duration of a pediatric migraine upon presentation to the emergency department?
   a. Seven days
   b. Six hours
   c. 24 hours
   d. Two days
5. Which dopamine receptor agonist has been most efficacious in treating migraine in pediatrics?
   a. Chlorpromazine
   b. Prochlorperazine
   c. Metoclopramide
   d. Promethazine

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Acute Treatment of Pediatric Migraine

Pediatric Migraine Criteria

Pediatric Migraine

At least five headaches meeting the following criteria:

- Untreated or unsuccessfully treated headache that lasts two to 72 hours
- Presence of two of the following headache characteristics:
  - Bilateral or unilateral location (usually frontotemporal)
  - Pulsating quality
  - Moderate to severe pain intensity
  - Aggravation by or causing patient to avoid routine physical activities
- During headache, at least one of the following symptoms:
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- Not better accounted for by another diagnosis according to the International Classification of Headache Disorders

Pediatric Migraine with Aura

At least two headaches meeting the following criteria:

- At least one of the following fully reversible aura symptoms: Visual, sensory, speech and/or language, motor, brainstem, or retinal
- Three or more of the following:
  - At least one aura symptom spreads gradually over five minutes
  - Two or more aura symptoms occur in succession
  - Each individual aura symptom lasts five to 60 minutes
  - At least one aura symptom is unilateral (aphasia is unilateral, dysarthria is not unilateral)
  - Aura accompanied by headache or followed by headache within 60 minutes
- Not better accounted for by another diagnosis according to the International Classification of Headache Disorders

Red Flags for Considering Neuroimaging for Headaches

Patient Characteristics

- Younger than 3 years of age
- Underlying medical conditions: sickle cell disease, immunodeficiency, malignancy, pregnancy, coagulopathy, congenital heart disease, recent head trauma, seizure disorder
- Neurocutaneous syndromes: ash-leaf spots, café-au-lait spots, petechial rash, port wine stain

Headache Characteristics

- Early-morning pattern or early-morning waking with headache, nausea, or vomiting
- Worsening headaches with straining
- Explosive new onset
- Occipital pain
- Progressive frequency and severity of the headache
- Associated changes in mood or mental status or deterioration in school performance

Signs/Symptoms

- Persistent vital sign changes, such as hypertension with bradycardia or fever
- Severe, persistent nausea and vomiting
- Lightheadedness, vertigo, or unsteadiness
- Perioral or extremity paresthesias or other localized weakness (may still represent aura for classic migraine)

Abortive Medications in the ED

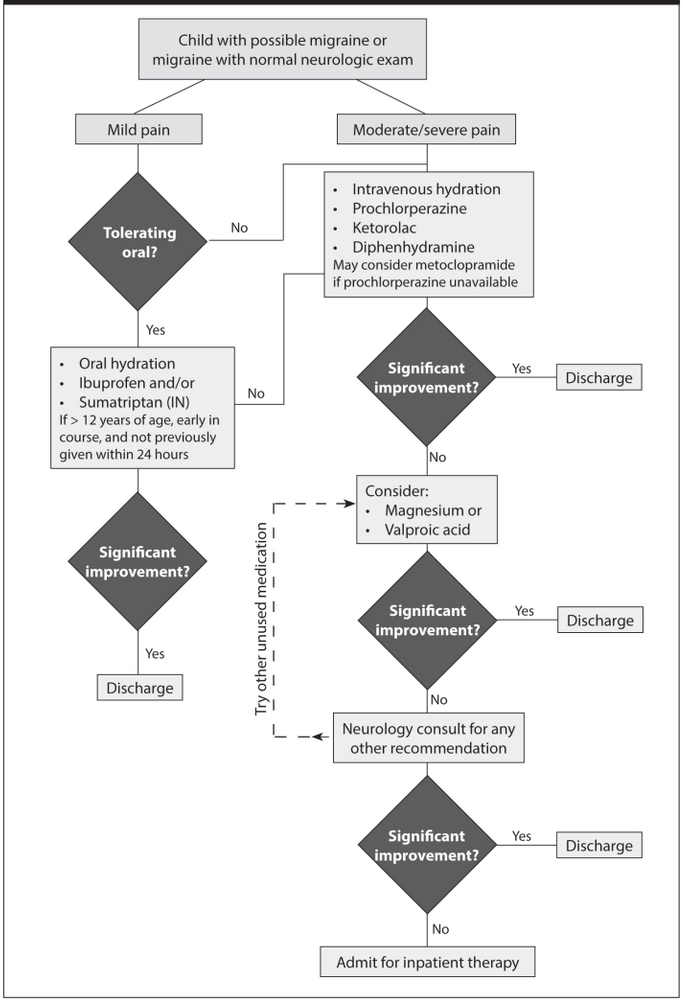
Drug	Dosing	Side Effects	Contraindications
Prochlorperazine Metoclopramide	0.15 mg/kg (IV), max 10 mg 0.1 mg/kg (IV), max 10 mg	Extrapyramidal side effects, sedation, prolong QT	Bone marrow depression
Sumatriptan	5 to 20 mg (IN)		History of stroke, cardiovascular disease, uncontrolled hypertension, hemiplegia, migraine
Ibuprofen Ketorolac	10 mg/kg, max 800 mg 0.5 mg/kg (IV), max 30 mg	Gastrointestinal upset	
Diphenhydramine	1 mg/kg, max 50 mg	Sedation	Platelet disorders
Magnesium	25 to 50 mg/kg, max 2 g	Nausea, vomiting, hypotension, flushing	
Valproic acid	15 mg/kg, max 1 g	Nausea, dizziness, tachycardia, paresthesia	Pregnancy, hepatic disease, mitochondrial disorders, metabolic disorders

IV: intravenously, IN: intranasally

Migraine Variants

Migraine Variant	Description	Symptoms/Characteristics
Migraine with brainstem aura (formerly known as basilar migraine)	• Migraine with aura symptoms originating from the brainstem • No retinal or motor symptoms	• Two or more of the following reversible symptoms: dysarthria, tinnitus, vertigo, hypacusis, diplopia, ataxia, and decreased consciousness
Chronic migraine	• Lasting > 90 days or very frequent migraine attacks that fulfill the criteria to the right	• Fifteen or more days of headache per month for three or more months • Five or more attacks fulfilling migraine or migraine with aura criteria • Eight or more days of headache per month for three months fulfilling migraine/migraine with aura criteria or perceived to be migraine at onset by patients and relieved by triptan or ergot derivative
Familial hemiplegic migraine	• Migraine with aura in patients with one or more first- or second-degree relatives with history of attacks fulfilling criteria for hemiplegic migraine • More common in children	• Motor weakness AND visual, sensory, and/or speech/language disturbances, all of which are fully reversible
Status migrainosus	• Debilitating migraine with or without aura that lasts 72 to 90 hours	• Disability caused by pain or other symptoms of migraine • Typical presentation of previous attacks, except for severity and duration
Cyclic vomiting syndrome	• Recurrent episodic attacks of severe nausea and vomiting that are self-limiting and have a predictable pattern • Patients are asymptomatic between episodes	• Nausea and/or vomiting lasting at least one hour and up to 10 days, with episodes occurring more than one week apart • Nausea and vomiting occurring more than four times per hour during the episodes
Abdominal migraine	• Five or more attacks of abdominal pain lasting two to 72 hours if untreated or unsuccessfully treated	• Pain is dull in quality and periumbilical, midline, or sometimes poorly located • Moderate to severe in intensity

Approach to Treating Pediatric Migraine Patients



Supplement to *Emergency Medicine Reports*, August 15, 2020: "Acute Treatment of Pediatric Migraine." Authors: Cecilia C. Guthrie, MD, FAAP, FACEP, Associate Professor, Department of Pediatrics, Section of Pediatric Emergency Medicine, The Children's Hospital at OU Medical Center, Oklahoma City; and Yashas Nathani, MD, Clinical Assistant Professor, Section of Pediatric Emergency Medicine, Department of Pediatrics, The Children's Hospital at OU Medical Center, Oklahoma City.