Publisher: American Academy of Pediatrics
Michael J. Held, Director, Division of Scholarly Journals and Professional Periodicals

Pediatrics in Review®
(ISSN 0191-9601) is owned and controlled by the American Academy of Pediatrics. It is published monthly by the American Academy of Pediatrics, 141 Northwest Point Blvd, Elk Grove Village, IL 60007-1098
Statements and opinions expressed in *Pediatrics in Review®* are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees. Recommendations included in this publication do not indicate an exclusive course of treatment or serve as a standard of medical care.
Subscription price for 2007 for print and online: AAP Fellow $154; AAP Candidate Fellow $144; Nonmember $194; Allied Health or Resident $144. Institutions call for pricing (866-843-2271). For overseas delivery, add $95. Current single issue price is $10 domestic, $12 international. Replacement issues must be claimed within 6 months from the date of issue and are limited to three per calendar year.
Periodicals postage paid at ARLINGTON HEIGHTS, ILLINOIS and at additional mailing offices.

POSTMASTER: Send address changes to PEDIATRICS IN REVIEW®, American Academy of Pediatrics Customer Service Center, 141 Northwest Point Blvd., Elk Grove Village, IL 60007-1098.
The printing and production of *Pediatrics in Review®* is made possible, in part, by an educational grant from Ross Products Division, Abbott Laboratories.

Answer Key: 1. C; 2. A; 3. D; 4. E; 5. D; 6. B; 7. C; 8. E; 9. B

contents

Pediatrics in Review® Vol.28 No.10 October 2007

Articles

363 Seizures in Children: Determining the Variation
Philippe Major, Elizabeth A. Thiele

372 Back to Basics: Congenital Nephrogenic Diabetes Insipidus
Michael A. Linshaw

381 Complementary, Holistic, and Integrative Medicine: Colic
Lawrence D. Rosen, Cecilia Bukutu, Christopher Le, Larissa Shamseer, Sunita Vohra

386 Pediatrics in the Community: Cap4Kids.org: Connecting Pediatricians to the Community at the Speed of Light
Daniel R. Taylor, C. Andrew Aligne

389 Index of Suspicion
Russell Hopp, Nagendra Natarajan, Mary L. Lewis, Karthik Krishnan, Warees T. Muhammad, James Logan

395 Question From the Clinician: Alternating Acetaminophen and Ibuprofen in the Treatment of Fever
Kami Jow, Janet R. Serwint

In Brief

396 Firearms

397 Pharmacokinetics

Internet-Only Article

Abstract appears on page 388.

e69 The Electronic Medical Record
Mark Simonian

Just follow these simple steps to activate your PREP® SA Online account:

1. Log on to PediaLink.org™ and move the pointer to the blue CME icon.
2. Click on the "Online" CME link.
3. Click the "Activate" button in the PREP® Self-Assessment Online section of the page.
4. Enter your PREP® ID number and complete the required information.

Cover: The artwork on the cover of this month's issue is by one of the winners of our 2005 Cover Art Contest, 9-year-old Jenny Samiec of Centerville, Ohio. Jenny's pediatrician is Anne Cata, MD.

Seizures in Children: Determining the Variation

Philippe Major, MD,*
Elizabeth A. Thiele, MD, PhD*

Author Disclosure
Dr Major did not disclose any financial relationships relevant to this article. Dr Thiele disclosed that she is a consultant to Abbott Laboratories.

Objectives

After completing this article, readers should be able to:

1. Classify the different seizure types.
2. Distinguish seizures from other paroxysmal phenomena.
3. List the possible causes of seizures according to age and mode of presentation.

Introduction

Seizures are among the most common pediatric neurologic disorders. The overall prevalence of epilepsy is approximately 1%, and as many as 5% of all children experience febrile seizures before the age of 6 years. Seizures are caused by an abnormal and excessive discharge of neurons, usually accompanied by behavioral or sensorimotor manifestations. Epilepsy is defined classically as the occurrence of two or more unprovoked seizures.

A seizure can be viewed as a symptom of an underlying central nervous system disorder that requires thorough evaluation and specific treatment. In addition to the consequences of the seizures, 50% of those who have epilepsy experience learning difficulties, and 30% to 50% have mental health and behavioral issues.

In this first of two articles on seizures in children, we review the diagnosis and classification of seizures as well as possible causes of seizures in childhood. The second article, to be published in the November 2007 issue of *Pediatrics in Review*, focuses on the laboratory diagnosis and management of seizure disorders.

Diagnosis and Causes of Seizures

The diagnosis of epilepsy and classification of specific seizure types are essential to determining a prognosis and choosing an appropriate treatment. The investigation of a child experiencing seizures begins with a medical history and physical examination. Although significant technologic advances have been made in electrophysiology and neuroimaging, the diagnosis of seizures and epilepsy remains largely clinical. Table 1 lists key features of the medical history and physical examination of a child presenting with paroxysmal events.

The first diagnostic step is to determine if the clinical presentation is compatible with seizures or with other paroxysmal phenomena. Although this distinction often is easy to make clinically, certain conditions (especially syncope, pseudoseizures, and tics) can be confused with seizures (Table 2). Syncope generally is preceded by dizziness, blurring of vision, feeling of imminent loss of consciousness, and pallor; seizures typically begin suddenly or are preceded by a brief specific aura. Syncope usually occurs during the daytime when the patient is in the upright position; seizures can occur at any time, in any position. Brief tonic or clonic movements sometimes follow syncope, but they are not classified as epileptic seizure activity.

Pseudoseizures should be suspected when the events are triggered by emotional disturbance or by suggestion, when the abnormal movements are not compatible with a typical seizure (pelvic thrusting, side-to-side head movement, forced eye closure), when the events occur most frequently during the daytime in the presence of other people, and when there is no postictal state. Tics are stereotyped, recurrent paroxysmal events that can be differentiated from seizures by the patient's ability to suppress them consciously.

When epilepsy is diagnosed, the cause remains unknown in 65% to 70% of patients. If no identifiable cause is determined following a complete investigation, the epilepsy is labeled

*Department of Neurology, Massachusetts General Hospital, Boston, Mass.

Table 1. Questionnaire and Physical Examination of the Patient Experiencing Paroxysmal Events

Questionnaire

- Handedness
- Pregnancy history: Ultrasonography results, infections, medications, alcohol use, cigarette smoking, drug abuse, trauma, prematurity
- Prenatal history: Labor duration, spontaneous vaginal delivery or cesarean section, birth difficulties (resuscitation, intubation), birthweight, head circumference at birth
- Development: Fine motor, language, gross motor, and social skills
- School functioning
- General medical history: Head trauma, meningitis, stroke
- Medications
- Family history: Epilepsy, febrile seizures, mental retardation
- Description of the events: aura; motor (myoclonic or clonic jerk, hypertonia, atonia, chewing movements), sensory (somesthetic, auditive, visual, gustatory), autonomic, or psychologic phenomena; automatisms; level of consciousness; tongue-biting; fecal or urinary incontinence; episode length; postictal state
- Age at event onset
- Event frequency
- Precipitating factors: Fever, sleep deprivation, stress, photosensitivity, drugs, alcohol withdrawal, or others
- Diurnal and nocturnal patterns
- Travel history
- Employment
- Driving

Physical Examination

- State of consciousness, language, social interactions
- Observation of the events (if possible); hyperventilation sometimes can provoke absence seizures
- Global development
- Dysmorphic features, limb asymmetry, neurocutaneous skin findings, organomegaly
- Head circumference
- Neurologic examination: Cranial nerves, motor strength and tone, osseotendinous reflexes, sensory and cerebellar function tests, gait

as "idiopathic" in patients who have normal development and physical findings. The epilepsy is labeled as "probably symptomatic" or "cryptogenic" in patients who have signs of abnormal brain function. When the seizures are the result of an identifiable brain lesion, the epilepsy is termed "symptomatic."

Table 2. Differential Diagnosis of Seizures (abbreviated list)

- Syncope
- Daydreaming
- Parasomnias
- Migraine
- Breath-holding spells
- Transient ischemic events
- Vestibular disorders
- Gastroesophageal reflux
- Movement disorders (tics, paroxysmal choreoathetosis)
- Psychotic hallucinations and delusions
- Nonepileptic events (pseudoseizures)
- Panic attacks

The potential causes of symptomatic epilepsy can be categorized as inherited genetic, congenital, and acquired (Table 3). Although the proportion of epilepsies of unknown cause remains stable at different ages, the causes of symptomatic epilepsies differ greatly, depending on the patient's age (Figure). In newborns, the most frequent symptomatic causes of epilepsy are brain malformations, infections, metabolic disorders (pyridoxine deficiency, hypoglycemia, hyponatremia, hypocalcemia, urea cycle disorders), hypoxic-ischemic encephalopathy, intracranial hemorrhage, and familial neonatal convulsions. In children, inherited metabolic or developmental diseases, idiopathic/genetic syndromes, infections, cortical dysplasias, and degenerative disorders may be causative. Symptomatic epilepsy in adolescents is caused pri-

Table 3. Causes of Symptomatic Epilepsy (abbreviated list)

Inherited Genetic

- Channelopathies, defined as mutations of neuronal ion channels (eg, one sodium channel defect is associated with benign familial neonatal seizures)
- Chromosomal abnormalities
  - —Trisomies 13, 18, 21, 22
  - —Deletion of chromosome 4p (Wolf-Hirschhorn syndrome)
  - —Partial 5p monosomy (cri du chat)
  - —Ring chromosome 14 and 20
- Mitochondrial DNA disorders
  - —Myoclonic epilepsy and ragged red fibers (MERRF)
  - —Mitochondrial myopathy, encephalopathy, lactic acidosis, strokelike episodes (MELAS)
- Metabolic disorders
  - —Aminoacidopathies
  - —Galactosemia
  - —Lysosomal lipid storage diseases (eg, Tay-Sachs)
  - —Leukodystrophies
  - —Mucopolysaccharidoses
  - —Peroxisomal disorders
  - —Pyridoxine deficiency
- Hereditary neurocutaneous disorders
  - —Tuberous sclerosis complex
  - —Neurofibromatosis
  - —Sturge Weber syndrome

Congenital (Inherited or Acquired)

- Developmental cortical malformations
- Cerebral tumor
- Vascular malformations
- Prenatal injury

Acquired

- Trauma
- Neurosurgery
- Infection
- Vascular disease
- Hippocampal sclerosis
- Tumors
- Neurodegenerative disorders
- Metabolic disorders
- Toxic disorders

marily by mesial temporal sclerosis, degenerative diseases, trauma, and tumors.

Classification of Epileptic Seizures

In 1981, the International League Against Epilepsy (ILAE) classified epilepsy according to partial or generalized seizure types (Table 4). The 1989 ILAE classification delineated specific epileptic syndromes (Table 5).

Partial seizures are caused by the abnormal activation of a limited number of neurons and are manifested by signs and symptoms that often allow clinical localization of the epileptic focus. Table 6 provides key features of partial seizure semiology. In contrast to simple partial seizures, complex partial seizures are associated with loss of consciousness. They also can be preceded by an aura and accompanied by various types of automatisms. Partial seizures generalize secondarily if the epileptic activity propagates to the entire brain.

Generalized seizures are caused by a global synchronous activation of neurons and always impair consciousness. Motor changes and electroencephalography (EEG) abnormalities are observed bilaterally in a grossly synchronous and symmetric pattern.

Typical absence seizures (formerly referred to as petit mal) are characterized by frequent, brief, abrupt losses of consciousness, often accompanied by eyelid flickering, that typically end abruptly with resumption of activity. The ictal EEG shows 3-Hz symmetric and synchronous spike and wave activity; the interictal tracing typically appears normal. Absence seizures occasionally can be induced by hyperventilation or photic stimulation. Although typical absence seizures are considered idiopathic, atypical absence seizures most frequently are associated with symptomatic or probably symptomatic epilepsies. Table 7 compares typical and atypical absence seizures.

Myoclonic seizures consist of brief contractions of a muscle, muscle group, or several muscle groups caused by a cortical discharge. Action, noise, startle, photic stimulation, or percussion sometimes can provoke such seizures. The ictal EEG shows generalized spike, spike and wave, or polyspike and wave discharges, often asymmetric or irregular and with frontal predominance.

Clonic seizures are characterized by jerking that often is asymmetric and irregular. Clonic seizures occur more frequently in neonates, infants, or young children. The ictal EEG shows fast activity (10 Hz), often mixed with higher-amplitude slow waves or polyspike and wave discharges.

Tonic seizures cause sustained muscle contraction without a clonic phase. They occur at any age and frequently are associated with diffuse cerebral damage and often are seen in children who have Lennox-Gastaut syndrome. The ictal EEG shows a flattening or attenuation of the background activity and fast activity (15 to 25 Hz), with increasing amplitude as the seizure progresses. The interictal EEG often shows generalized epileptic discharges.

Tonic-clonic seizures (grand mal) are characterized

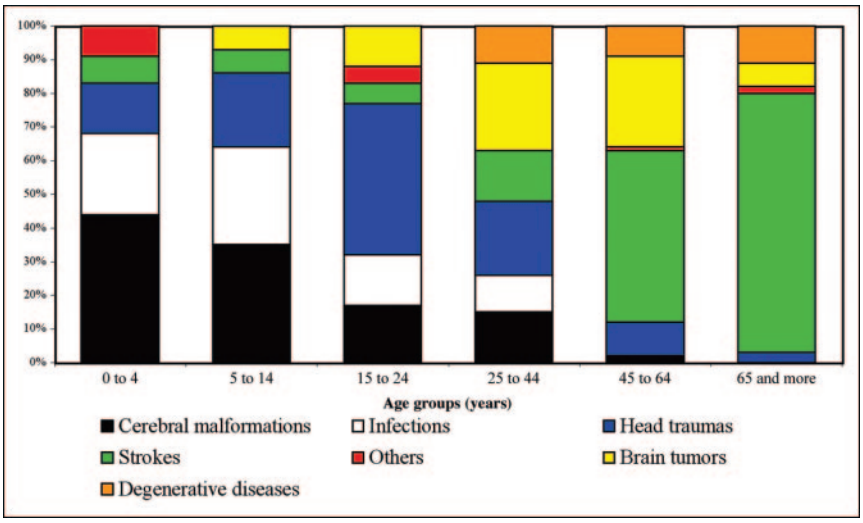


Figure. Proportional incidences for symptomatic epilepsies according to age and etiology. Adapted from Annegers JF. The epidemiology of epilepsy. In: Willie E, ed. *The Treatment of Epilepsy: Principles and Practice.* Philadelphia, Pa: Lea & Febiger; 2001:135.

by three successive phases: tonic, clonic, and postictal. The tonic phase typically lasts 10 to 30 seconds and is associated with desynchronization or attenuation on EEG. The seizure progresses to a clonic phase that lasts 30 to 60 seconds in which bursts of faster activity are seen on the EEG. The postictal period usually consists of a state of confusion and fatigue for 2 to 30 minutes and is characterized by diffuse slowing on EEG.

Epileptic Syndromes

The 1989 ILAE classification defines epileptic syndromes (Table 5) by the association of specific clinical, electroencephalographic, and imaging characteristics. Of the several epilepsy syndromes, many are associated with significant neurologic impairment. Following are descriptions of some of the most frequent types of epilepsies and epilepsy syndromes in childhood. Specific treatments for these conditions are discussed in the second article.

Major Focal (Partial) Epilepsies

Benign partial epilepsy with centrotemporal spikes (also called benign rolandic epilepsy) is the most common partial epilepsy syndrome in children. The typically affected child presents between 3 and 13 years of age with partial seizures characterized by tonic or clonic activity and paresthesias of the lower face, which often are unilateral and associated with drooling and dysarthria. Seizures are infrequent, commonly occur nocturnally, and rarely become secondarily generalized. The EEG shows characteristic unilateral or bilateral centrotemporal high-voltage sharp waves activated by drowsiness and sleep. Neuroimaging studies should be performed to rule out other disorders, such as parasagittal tumors.

Temporal lobe epilepsy generally begins with partial seizures in childhood, followed by a seizure-free period until adolescence, when seizures reappear. A history of febrile seizures (mostly atypical) is found in about 35% of patients who have intractable temporal lobe epilepsy. Seizures frequently are preceded by an aura (epigastric discomfort, déjà vu ["already seen"], déjà entendu ["already heard"]), psychic symptoms such as fear, or automatisms (oroalimentary repetitive movements, vocalizations). Compared with frontal lobe epilepsy, secondary generalization happens less often and seizures occur less frequently.

Frontal lobe epilepsy is characterized by short (10 to 30 sec), frequent partial seizures that tend to occur in clusters, mostly at night. A familial history of frontal lobe seizures sometimes is found. The auras are nonspecific. Automatisms may be bizarre (eg, pedaling movements) and sometimes are mistaken for nonepileptic events. Aversive head and eye deviation may occur. A jacksonian motor seizure (the spread of clonic movements that progresses along contiguous body parts in a pattern corresponding to the body representation on the primary motor strip) sometimes is observed. Complex partial status epilepticus occurs relatively frequently. Postictal Todd paralysis (transient paralysis following a seizure) sometimes is noted, particularly if the seizure focus is located near the motor cortex.

Parietal lobe epilepsy generally causes simple partial seizures with somatosensory symptoms such as paresthesias (sometimes painful), apraxia, and distortion of body image. Visual phenomena consisting of well-formed hallucinations sometimes are reported; pictures of people, animals, or scenes may be perceived. A receptive type of aphasia can occur if the epileptic activity is located on the dominant hemisphere.

Occipital lobe epilepsy is characterized by simple elementary visual symptoms, such as patterns or flashes of light or colors. Contralateral eye deviation and ictal blindness also are described.

Table 4. International Classification of Epileptic Seizures

Partial (Focal, Localized) Seizures

- Simple partial seizures
  - —With motor signs
  - —With somatosensory or special sensory systems
  - —With autonomic symptoms and signs
  - —With psychic symptoms
- Complex partial seizures
  - —Simple partial onset followed by impairment of consciousness
  - —With impairment of consciousness at onset
- Partial seizures evolving to secondarily generalized seizures
  - —Simple partial seizures evolving to generalized seizures
  - —Complex partial seizures evolving to complex partial seizures evolving to generalized seizures

Generalized Seizures (Convulsive or Nonconvulsive)

- Absence seizures
  - —Typical absences
  - —Atypical absences
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Tonic-clonic seizures
- Atonic seizures

Unclassified Epileptic Seizures

Adapted from the Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22:489–501.

Major Generalized Idiopathic Epilepsy Syndromes

Childhood absence epilepsy begins between 3 and 10 years of age in cognitively normal children. Numerous seizures can occur every day. The EEG shows classic ictal generalized 3-Hz spike-and-wave discharges lasting 5 to 10 seconds superimposed on a typically normal interictal background. Photic stimulation and hyperventilation are well-known precipitating factors.

Juvenile absence epilepsy develops around puberty and is associated with less frequent seizures compared with childhood absence epilepsy. Approximately 80% of patients experience tonic-clonic seizures in addition to their absences. A genetic predisposition is observed. The EEG shows generalized spike-and-wave discharges.

Juvenile myoclonic epilepsy (Janz syndrome) typically begins between 8 and 18 years of age (peak incidence, 15 years old) and usually is characterized by upper limb myoclonic jerks that occur after waking ("morning myoclonus"). Generalized tonic-clonic seizures also occur frequently; many patients experience absence seizures. Sleep deprivation, alcohol, hyperventilation, and photosensitivity are common triggers. A family history of epilepsy is found in 40% of cases. Cognition and neurologic findings are normal. The EEG shows generalized 4 to 6-Hz polyspikes and spike-and-wave epileptic discharges with normal background activity.

Benign neonatal convulsions are characterized by short tonic, clonic, or apneic seizures that begin between 2 and 5 days after birth in neurologically normal infants. The prognosis generally is good, but 15% of patients develop epilepsy in the future. Familial autosomal dominant and sporadic cases are described. In familial cases, seizures occur on the second or third day after birth, and the EEG has no specific pattern. In comparison, seizures in sporadic cases begin at around the fifth postnatal day and show theta bursts on the EEG.

Major Generalized Symptomatic Epilepsy Syndromes

Infantile spasms usually start during the first postnatal year (typically 5 to 12 months of age) and are characterized by symmetric, bilateral, brief, and sudden contractions of the axial muscle groups. The features of the spasms depend on whether the flexor or extensor muscles are predominantly affected. Spasms tend to occur in clusters soon after awakening or on falling asleep. Sudden loud noises or tactile stimulation, but not photic stimulation, may precipitate them. The frequency of spasms varies from only a few times a day to several hundred a day. Periods of attenuated responsiveness may follow a spasm. Children who have infantile spasms often show hypsarrhythmia on EEG, which is a profoundly disorganized background of high-amplitude waves and multifocal spikes. Infantile spasms can be classified as symptomatic, cryptogenic, or idiopathic. The symptomatic group accounts for 75% of cases. Evaluating children for possible tuberous sclerosis complex is critical because this is the single most common cause. Early control of spasms with medication is associated with a better cognitive outcome. Without treatment, spasms tend to disappear spontaneously before 3 years of age. However, as many as 60% of children who have infantile spasms develop other seizure types and epileptic syndromes, such as Lennox-Gastaut syndrome. Also, most children who develop infantile spasms experience significant neurocognitive sequelae.

Table 5. International Classification of Epilepsies, Epileptic Syndromes, and Related Seizure Disorders

Localization-related (Focal, Local, Partial)
- Idiopathic (primary)
  - —Benign childhood epilepsy with centrotemporal spikes
  - —Childhood epilepsy with occipital paroxysms
  - —Primary reading epilepsy
- Symptomatic (secondary)
  - —Temporal lobe epilepsies
  - —Frontal lobe epilepsies
  - —Parietal lobe epilepsies
  - —Occipital lobe epilepsies
  - —Chronic progressive epilepsia partialis continua of childhood
  - —Syndromes characterized by seizures that have specific modes of precipitation
- Cryptogenic, defined by
  - —Seizure type
  - —Clinical features
  - —Anatomic localization

Generalized
- Idiopathic (primary)
  - —Benign neonatal familial convulsions
  - —Benign neonatal convulsions
  - —Benign myoclonic epilepsy in infancy
  - —Childhood absence epilepsy (pyknolepsy)
  - —Juvenile absence epilepsy
  - —Juvenile myoclonic epilepsy (Janz syndrome)
  - —Epilepsies with grand mal seizures on awakening
  - —Other generalized idiopathic epilepsies
  - —Epilepsies with seizures precipitated by specific modes of activation
- Cryptogenic or symptomatic
  - —West syndrome (infantile spasms)
  - —Lennox-Gastaut syndrome
  - —Epilepsy with myoclonic-astatic seizures
  - —Epilepsy with myoclonic absences
- Symptomatic (secondary)
  - —Nonspecific cause
    - –Early myoclonic encephalopathy
    - –Early infantile epileptic encephalopathy with suppression burst
    - –Other symptomatic generalized epilepsies
  - —Specific syndromes
    - –Epileptic seizures may complicate many disease states

Undetermined Epilepsies
- With both generalized and focal seizures
  - —Neonatal seizures
  - —Severe myoclonic epilepsy in infancy (Dravet syndrome)
  - —Epilepsy with continuous spike and waves during slow-wave sleep
  - —Acquired epileptic aphasia (Landau-Kleffner syndrome)
  - —Other undetermined epilepsies
- Without unequivocal generalized and focal features

Special Syndromes
- Situation-related seizures
  - —Febrile convulsions
  - —Isolated seizures or isolated status epilepticus
  - —Seizures occurring only with an acute or toxic event, due to factors such as alcohol, drugs, eclampsia, and nonketotic hyperglycemia

Adapted from Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for a revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389–399.

Lennox-Gastaut syndrome is a condition characterized by the clinical triad of diffuse slow spikes and waves on EEG, mental retardation, and multiple types of generalized seizures, especially atypical absences and tonic and atonic seizures. The disorder can be classified as symptomatic or cryptogenic; 70% of patients are symptomatic, 33% of whom have had infantile spasms. The age of onset is between 2 and 8 years. The prognosis is poor for neurocognitive outcome and seizure control, particularly in symptomatic cases. With age, the intellectual quotient tends to deteriorate and the tonic seizures persist, but the slow spike-and-wave pattern tends to resolve.

Febrile seizures occur in 5% of children between the ages of 3 months and 6 years. A familial predisposition sometimes is present. The distinction between typical and atypical febrile seizures influences the management and determines the prognosis (Table 8). Typical febrile seizures are considered benign, but can recur in up to 30% to 50% of children, especially if the first seizure occurred during the first year after birth. Such seizures do not increase the risk of future epilepsy significantly. In contrast, 2% to 13% of children who have atypical febrile seizures subsequently develop epilepsy.

When a child presents immediately after a febrile seizure, the goal is to identify a possible infectious source. Usually, no ancillary testing is required for simple febrile seizures, although magnetic resonance imaging or computed tomography scan often is indicated for patients having atypical febrile seizures to evaluate for focal dis-

Table 6. **Partial Seizure Semiology**

Types of Manifestations	Description of the Clinical Manifestations	Brain Regions Involved
Motor	Jerking of extremities	Frontal or central lobes
Somatosensory or special sensory	Tingling or numbness	Central or parietal lobes
	Simple visual phenomena	Calcarine cortex (occipital)
	Rising epigastric sensation	Mesial temporal lobe
Autonomic	Changes in skin color, blood pressure, heart rate, pupil size, piloerection	Frontal or temporal lobes
Psychic	Dysphasia or aphasia	Frontal or temporoparietal regions
	Dysmnestic symptoms (flashbacks, déjà-vu, jamais vu, or panoramic experiences)	Mesial temporal lobe
	Cognitive symptoms (dreamy state, sensations of unreality or depersonalization)	Temporal lobe
	Affective symptoms (fear, depression, anger, irritability)	Mesial temporal lobe
	Illusions of perception (size [macro- or micropsia], shape, weight, distance, sound)	Temporal or temporoparietal regions
	Structured hallucinations (visual, auditory, gustatory, olfactory)	Temporal or parietooccipital regions

ease. A lumbar puncture should be performed if meningitis is suspected. Most experts agree that EEG is not required because it does not predict seizure recurrence or the development of epilepsy. Parental reassurance and education are crucial.

Status epilepticus is a neurologic emergency defined traditionally as a continuous seizure or the occurrence of serial seizures, between which there is no return of consciousness, lasting more than 30 minutes. Many experts now suggest that the time threshold should be reduced to 15 minutes or less to heighten the urgency for treatment. Experimental models have shown that a continuous seizure lasting more than 30 minutes potentially can harm the brain. Excessively increased metabolic demand by constantly discharging neurons produces regional oxygen insufficiency that causes cell damage and necrosis. Three major subtypes of status epilepticus can occur in children: prolonged febrile seizures, idiopathic status epilepticus, and symptomatic status epilepticus. The last subtype is associated with the most morbidity and mor-

Table 7. **Comparison of Typical and Atypical Absence Seizures**

Factor	Typical	Atypical
Age of onset	Childhood	Any age
Onset/offset of seizure	Abrupt	Often gradual
Consciousness	Totally lost	Often partially impaired
Other clinical features during seizure	Slight (eye flickering)	Can be prominent, including aura, automatism
Duration of seizures	Short (usually <10 sec)	Long (usually several minutes)
Frequency of seizures	Numerous, frequently in clusters	Usually less frequent
Postictal	None	Confusion, headache, emotional disturbance are common
Coexisting seizure types	Sometimes tonic-clonic and myoclonic	Mixed seizure disorder is common; all seizure types
Cause	Idiopathic generalized epilepsy	Any focal pathology or probably symptomatic epilepsy
Underlying focal anatomic lesion	None	Limbic structures, neocortex
Other neurologic signs and symptoms	None	Usually learning difficulties
Ictal EEG appearance	3-Hz spike and wave	2 to 2.5-Hz spike and wave
Interictal EEG appearance	Usually normal	Abnormal

Table 8. Characteristics of Typical Febrile Seizures

- Seizure occurrence between ages 3 months and 6 years of age
- Normal development and normal neurologic examination findings
- Duration <15 min
- Generalized tonic-clonic seizure
- Only one seizure during one febrile episode
- No postictal deficit (eg, Todd paralysis)
- Not caused by a central nervous system infection

tality; the cause of death usually is attributed directly to the underlying abnormality. The mortality associated with status epilepticus is approximately 5%.

Conclusion

Seizures occur frequently in the pediatric population. They have protean clinical manifestations, and the causes are age-dependent. Knowledge of the seizure classification is important to determine appropriate prognosis and treatments.

ACKNOWLEDGMENTS. We are very thankful to Dr Ron Thibert for his help in the preparation of this article.

Suggested Reading

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for a revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22:489–501

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389–399

Committee on Quality Improvement, Subcommittee on Febrile Seizures. Practice parameter: long-term treatment of the child with simple febrile seizures. *Pediatrics*. 1999;103:1307–1309

Growing Up With Epilepsy. (an educational resource on childhood epilepsy created by the MGH pediatric epilepsy program in collaboration with the WBGH Educational Foundation). Available at: www.massgeneral.org/childhoodepilepsy

Hirtz D, Ashwal S, Berg A, et al. Report of the Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. Practice parameter: evaluating a first nonfebrile seizure in children. *Neurology*. 2000;55:616–623

Hirtz D, Berg A, Bettis D, et al. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Practice parameter: treatment of the child with a first unprovoked seizure. *Neurology*. 2003;60:166–175

Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. Practice parameter: the neurodiagnostic evaluation of the child with a first simple febrile seizure. *Pediatrics*. 1996;97:769–775

Sharma S, Riviello JJ, Harper MB, et al. The role of emergent neuroimaging in children with new-onset afebrile seizures. *Pediatrics*. 2003;111:1–5

PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. Which of the following is the *most* likely cause of symptomatic epilepsy in the adolescent population?

   A. Cortical dysplasia.
   B. Genetic syndromes.
   C. Head trauma.
   D. Hypoxic-ischemic encephalopathy.
   E. Pyridoxine deficiency.

2. A 10-year-old boy is brought to your clinic because his mother is worried about seizures. She reports that for the last few weeks, he calls out to wake her frequently at night because of numbness of one side of his mouth associated with twitching and drooling. He remains conscious during the episodes, and they last approximately 2 minutes. His neurologic examination and brain magnetic resonance imaging results are normal. Of the following, which is the *most* likely finding on electroencephalography?

   A. Centrotemporal high-voltage spike discharges.
   B. Continuous focal spike discharges that spread to a mirror focus on the other side.
   C. High-amplitude waves and multifocal spikes.
   D. Normal findings.
   E. 3-Hz spike-and-wave discharges.

3. A 5-month-old girl is brought to the emergency department because of jerking episodes for the past 2 weeks. Her mother reports bilateral jerking of the arms and neck flexion that last for a few seconds. The episodes are more frequent in the morning right after she wakes up. She seems fine between episodes, with normal activity and appetite. The infant appears well, has normal findings on physical examination, and has no skin lesions. Electroencephalography shows a disorganized background with high-amplitude waves and multifocal spikes. Of the following, the *most* likely diagnosis is:

   A. Absence epilepsy.
   B. Benign myoclonus of infancy.
   C. Frontal lobe epilepsy.
   D. Infantile spasms.
   E. Lennox Gastaut syndrome.

4. A 4-year-old girl who has a family history of epilepsy comes to the neurology clinic with a history of spells for 5 months. Her mother reports that the episodes consist of unilateral arm jerking for a few seconds but no loss of consciousness. The girl often reports feeling afraid before the episodes start. Findings on her neurologic examination are normal. Of the following, the *most* likely diagnosis is:

   A. Absence epilepsy.
   B. Benign rolandic epilepsy.
   C. Generalized idiopathic epilepsy.
   D. Juvenile myoclonic epilepsy.
   E. Temporal lobe epilepsy.

BACK TO BASICS

A review of the scientific foundations of current clinical practice

Author Disclosure
Dr Linshaw did not disclose any financial relationships relevant to this article.

Congenital Nephrogenic Diabetes Insipidus

Michael A. Linshaw, MD*

Objectives

After completing this article, readers should be able to:

1. Recognize the clinical features of congenital nephrogenic diabetes insipidus
2. Know the different hereditary patterns of nephrogenic diabetes insipidus.
3. Discuss how to evaluate a child who has hypernatremic dehydration in the presence of dilute urine.
4. Describe the nutritional, fluid, and pharmacologic goals of therapy.

Introduction

Diabetes insipidus (DI), the inability under physiologic conditions to concentrate urine adequately, is characterized by the passage of large amounts of very dilute urine, even as the body is threatened with progressive dehydration and circulatory collapse in the presence of severe hypernatremia. Normally, about 10% to 12% of glomerular-filtered volume is reabsorbed along distal nephron vasopressin (ADH)-sensitive sites. Such reabsorption is accomplished by a responsive tubule exposed to ADH that has been secreted by stimulation of osmotic or volume receptors. Both the absence or insufficiency of ADH due to pituitary or hypothalamic dysfunction (central diabetes insipidus [CDI]) or the failure of the kidney to respond adequately to normal or high serum concentrations of ADH (nephrogenic diabetes insipidus [NDI]) can present with similar clinical features, most notably polyuria, polydipsia, and extreme thirst.

The seriousness of such a defect can be illustrated by considering a child who has an actual glomerular filtration rate of 50 mL/min. Failure to reabsorb the expected approximately 5 to 6 mL/min along ADH-sensitive sites would result in the potential loss of 300 to 360 mL/h of fluid or approximately 1 L in 3 hours. With progressive dehydration, the glomerular filtration rate would decline and blunt the fluid loss to some extent, but ensuing volume depletion, hypernatremia from water loss, and renal insufficiency could become life-threatening.

CDI occurs as a result of intracranial lesions; NDI is caused by defects in the renal concentrating process (Table 1). In NDI, congenital X-linked or autosomal inherited forms of DI generally are more severe, although occasional mild phenotypes have been described. This article focuses on congenital nephrogenic diabetes insipidus (CNDI). The family history usually is positive, but generations may be skipped, and cases may occur de novo.

Case Report

A 3,600-g male infant was born following a normal pregnancy and delivery. He was breastfed and appeared healthy, although his height and weight had fallen approximately four growth curves to the 5th percentile by

*Associate Professor of Pediatrics, Harvard Medical School; Department of Pediatrics-Division of Pediatric Nephrology, Massachusetts General Hospital for Children, Boston, Mass.

Table 1. Causes of Diabetes Insipidus

Central (Hypothalamic/pituitary Lesions Leading to Insufficient Production or Release of ADH)

- Postoperative brain surgery
- Intracranial lesions (cysts, aneurysms, tumors of pituitary, brainstem)
- Infiltrative malignancies (lymphoma, leukemia)
- Infections, including encephalitis, meningitis, abscess
- Head trauma
- Hypoxic injury
- Congenital, inherited as an autosomal dominant disorder

Nephrogenic (Renal Resistance to ADH from Lesions Interfering With the Renal Concentrating Mechanism)

- Acquired metabolic aberrations
  - —Hypokalemia (chronic, Bartter syndrome)
  - —Hypercalcemia
  - —Hypercalciuria (rare)
  - —Diabetes mellitus
- Medullary damage
  - —Chronic pyelonephritis
  - —Infiltrative disease (leukemia, lymphoma, amyloidosis)
  - —Sickle cell disease
  - —Cystinosis
  - —Other forms of chronic renal failure
  - —Obstructive uropathy
- Drugs (lithium, demeclocycline, amphotericin B, diphenylhydantoin)
- Inherited
  - —X-linked
  - —Autosomal recessive
  - —Autosomal dominant

4 months of age, at which point he was introduced to formula. He began to vomit several times a day; cried unless given water; soaked 10 to 12 diapers daily; developed hard, pebble-like stools; and was able to suck 12 to 15 wet cloths daily until dry. He took at least 78 oz of fluid a day, with a clear preference for water. Despite dietary changes, he refused solid foods, demanded more water, developed hypernatremic dehydration, and stopped growing. By 8 months of age, his height and weight had fallen well below the 5th percentile.

When referred at 10½ months of age, he was irritable and chronically dehydrated but normotensive. He had dry skin, sunken eyes without skin tenting, slightly moist mucous membranes, and several palpable hard, mobile abdominal masses, presumed to be hard stool. Serum sodium was 155 mEq/L (155 mmol/L), potassium was 5.2 mEq/L (5.2 mmol/L), chloride was 119 mEq/L (119 mmol/L), and bicarbonate was 21 mEq/L (21 mmol/L). Blood urea nitrogen measured 83 mg/dL (29.6 mmol/L), creatinine was 0.8 mg/dL (70.7 mcmol/L), calcium was 10.4 mg/dL (2.6 mmol/L), and phosphorus was 6.6 mg/dL (2.1 mmol/L). Initial serum and urine osmolalities were 343 and 172 mOsm/L, respectively. After oral rehydration and correction of hypernatremia and azotemia, the patient underwent a water deprivation test. After 12 hours, he had lost 5% of his body weight from persistent polyuria, and his serum and urine osmolalities were 326 and 320 mOsm/L, respectively. There was no response to administration of vasopressin. His polyuria continued, and the serum and urine osmolalities rose to 338 and 326 mOsm/L, respectively.

The family preferred to avoid possible adverse effects of pharmacotherapy, and calculations were made to provide adequate calories and water to offset estimated insensible water losses and to allow the relatively low renal solute load to be excreted in urine that had an osmolality of 80 to 120 mOsm/L. Adjustments were made as the child grew. Solid foods were introduced and formula phased out at 15 to 16 months of age. By 24 months of age, his height had reached the 5th percentile, but his weight had increased disproportionately with overzealous feeding. His caloric intake was reduced. (1) With convenient access to water, he regulated his water needs effectively day and night, adjusted well to school, and turned out to be intellectually gifted.

Clinical Features

Children who have CNDI can develop signs in the first weeks after birth, but such signs may not be apparent to parents or practitioners, especially if the baby is breastfeeding, because human milk has a low renal solute load and signs of dehydration may not be appreciated immediately. However, affected infants prefer water, if available, and often are irritable and hard to mollify, demonstrating frequent, almost constant, crying, even in the mother's arms. They improve dramatically if given water and periodically are febrile without good reason. Clinical findings progress over time, varying with the degree of dehydration (Table 2).

Affected infants have marked polyuria; excrete very dilute urine; develop small, hard, pebble-like stools; fall off growth chart percentiles; and are anxious to suck, although they want to drink, not feed. Given moist towels, they will suck the towels dry. Diapers are saturated, dripping, and heavy and need frequent changing.

Physical findings vary with the degree of dehydration. The serum sodium concentration often is greater than 160 mEq/L (160 mmol/L), with acidosis. The blood urea nitrogen value usually is elevated out of proportion to a high serum creatinine concentration, as is typical of prerenal failure resulting from effective volume depletion. Urine specific gravity or osmolality often is less than 1.005 or 150 mOsm/kg water, respectively, despite hypernatremia.

Mental retardation can result

Table 2. Clinical Findings in Congenital Nephrogenic Diabetes Insipidus

Historical Features

- Failure to thrive
- Extreme thirst
- Unexplained fever
- Irritability
- Constipation
- Impressive polyuria
- Vomiting
- Seizures

Physical Findings

- Dry mouth and eyes
- Poor skin turgor
- Sunken eyes and anterior fontanelle
- Mottled skin
- Decreased peripheral pulses
- Low blood pressure
- Multiple abdominal masses/fecaliths

Laboratory Features

- Hypernatremia
- Hyperchloremia
- Metabolic acidosis
- Normal potassium concentration
- Hyperuricemia
- High serum and low urine osmolality

from repeated episodes of severe hypernatremic dehydration, but is not a fundamental part of the clinical picture. Studies of cognitive function in patients who have CNDI showed that most of the children had normal intelligence. (2)

Large urinary volumes may be associated with nonobstructive hydronephrosis and hydroureter, sometimes severe. Urinary tract infections, enuresis, daytime incontinence, urinary retention, and traumatic rupture of the urinary tract are potential complications. Dysfunction may be severe enough to resemble a neurogenic bladder. Growth failure is related to inadequate caloric intake because of the constant large fluid intake needed to maintain electrolyte balance. No reliable evidence indicates that growth will be retarded in such children when they are given early and adequate caloric and fluid intake. However, during the early years, before children had ready access to water, extreme diligence was required of caregivers, even with pharmacotherapy, to maintain growth and health.

Table 3. Pathogenesis and Genetics of Nephrogenic Diabetes Insipidus

Mode of Transmission	Gene	Target Site of Action
X-linked	*Xq28*	Vasopressin 2 Receptor (V2R)
Autosomal	*12q13*	Aquaporin 2 (ADH-sensitive) water channel

Genetic Pathogenesis

CNDI occurs in X-linked and autosomal recessive and dominant modes of inheritance. Mutations in two different, but functionally related, genes cause clinically similar disease (Table 3). Defects in a gene on the X chromosome encoding the vasopressin receptor 2 (VR2) are carried by females, who can have variable (rarely severe) degrees of polydipsia and polyuria. Males tend to have more serious symptoms. The VR2 is present on basolateral membranes of collecting tubule principal cells. When circulating ADH binds to this receptor, cascading chemical changes (activation of G-protein and adenylyl cyclase, generation of cyclic AMP, activation of protein kinase A) ultimately lead to insertion of cytoplasmic water channels (aquaporins) directly into the apical membrane. This occurrence facilitates water reabsorption down an osmotic gradient (see later brief discussion of countercurrent movement of fluid and solutes).

About 90% of children born with CNDI have loss-of-function mutation defects in the VR2, with more than 180 VR2 gene mutations reported. In most of these mutations, the defective protein is retained in the cellular endoplasmic reticulum and cannot reach the cell membrane. In other mutations, the protein reaches the cell membrane, but cannot bind ADH or activate the G-protein/cyclic AMP chemical cascade.

About 10% of children who have CNDI have defects in the gene encoding the aquaporin 2 (AQP2) ADH-sensitive water channel located on chromosome 12. Most of these patients show autosomal recessive inheritance, with mutant genes causing misfolding of the water channel protein so the channel is trapped in the endoplasmic reticulum, fails to route to the apical membrane, and degrades quickly. Some channel mutations may cause less severe misfolding and may be partly functional, causing less severe polyuria.

In those who have autosomal dominant disease, the least common type of CNDI, the mutation appears to be located in the COOH terminus of the protein. These water channels move to other parts of the cell and are

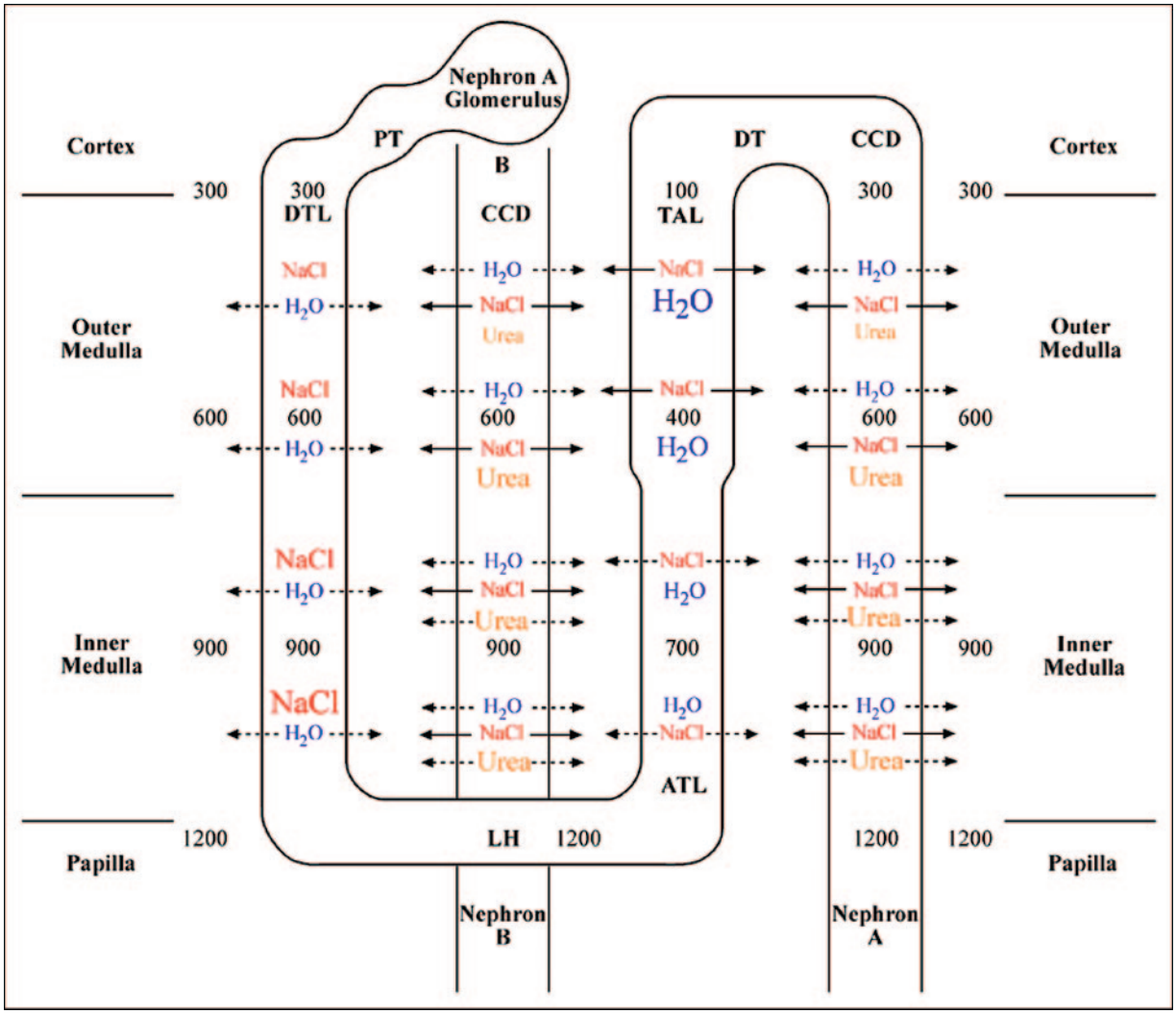


Figure. Solute and water transport during the urinary concentrating process. Solid arrows depict active NaCl transport; dashed arrows depict passive transport. Decreased permeability to NaCl, urea, or H_2O is illustrated by lack of arrows in the appropriate segment. Low urea permeability in the outer medulla is reflected by lack of arrows for urea, and increased urea permeability from the effect of ADH in the medullary portion of the collecting duct is shown by arrows. Numbers show osmolality in mOsm/kg H_2O. Increasing NaCl concentration in the descending limb, caused by removal of H_2O from this segment that has low NaCl permeability, is depicted by larger lettering for NaCl. Increasing H_2O concentration (dilute urine) in the ascending limb, caused by NaCl transport from this segment that has low H_2O permeability, is depicted by larger lettering for H_2O. Isotonic reabsorption of NaCl and H_2O in proximal and distal tubules to maintain cortical isotonicity is assumed in this illustration. A CCD with its medullary portions from a second nephron (B) is placed between the descending and ascending limbs of nephron A to illustrate more clearly the effect of solute and H_2O movement from the CCD on solute and H_2O transfer occurring in the limbs. See text for more details. Not illustrated or discussed is a recycling of urea from interstitium to ATL and DTL. ADH=antidiuretic hormone, ATL=ascending thin limb, CCD=cortical collecting duct, DT=distal tubule, DTL=descending thin limb, H_2O=water, LH=loop of Henle, NaCl=sodium chloride, PT=proximal tubule, TAL=thick ascending limb.

retained by lysosomes via the Golgi apparatus, stored in other vesicles, or routed to the basolateral rather than the apical membrane.

Pathophysiology

The Figure illustrates the sequences described in the following section. Fluid filtered at the glomerulus enters the proximal tubule essentially isotonic with serum. Water and solute are reabsorbed isotonically along this segment, but fluid traversing the

descending loop of Henle is exposed to an increasing interstitial osmolality largely generated by events occurring in the ascending thick limb. Therefore, it is helpful to consider this tubular segment initially to appreciate development of the corticomedullary osmotic gradient.

The ascending thick limb has an apical membrane Na-K-2Cl cotransporter and an active Na+ pump (basolateral Na+/K+-ATPase). However, its water permeability is low because it lacks water channels. In this segment, salt is reabsorbed in the relative absence of water, resulting in tubular fluid that becomes progressively hypotonic as the surrounding interstitial sodium chloride (NaCl) concentration increases. Fluid reentering the cortex becomes isotonic from continued salt and water reabsorption as it reaches the collecting duct.

In the presence of ADH, the cortical collecting duct is highly permeant to water, but relatively nonpermeant to urea. Therefore, fluid descending the collecting duct loses water osmotically (from a high interstitial NaCl content generated by the thick ascending limb), but the urea concentration increases. By contrast, the medullary collecting duct is highly permeant to both urea and water in the presence of ADH. Accordingly, tubular fluid urea diffuses into the interstitium down a concentration gradient. The accumulating interstitial urea raises medullary interstitial osmolality that, in turn, affects fluid in the descending loop of Henle. This segment is highly permeant to water, less so to urea, and relatively impermeant to salt.

Therefore, as descending loop fluid traverses an interstitium enriched with NaCl (from thick ascending limb active transport), water is abstracted and tubular fluid NaCl concentration increases. The abstracted water may dilute interstitial urea to some extent. As fluid enters the deeper medulla, the higher interstitial urea concentration from medullary collecting duct reabsorption helps abstract more water from the descending loop to increase its osmolality and NaCl concentration further. The abstracted water also dilutes the deeper medullary interstitial NaCl concentration.

As fluid ascends the thin limb, a favorable gradient is created for NaCl reabsorption into the interstitium. The resulting added NaCl in the deeper medulla helps facilitate more water reabsorption from the medullary collecting duct fluid as it descends further in the medulla. The thin ascending limb is relatively impermeant to water because it also lacks water channels. Therefore, as fluid enters the thin ascending limb and heads toward the cortex, the interstitial salt concentration is decreasing, favoring reabsorption of salt.

Water does not leave this segment effectively. Lack of water channels accounts for the eventual hypotonicity of urine as it leaves the ascending loop of Henle. However, because of ADH-induced high water and urea permeability of medullary collecting ducts, equilibration of osmolality results in a final urine that has a concentration similar to that of fluid at the bend of the loop of Henle and the deep medullary interstitium. This process translates to a roughly fourfold increase (multiplication) in urinary osmolality, from approximately 300 mOsm/kg in the cortex to approximately 1,200 mOsm/kg or more at the medullary papillary tip by the time a child reaches 1 to 2 years of age.

In older children and adults, approximately 50% of the urinary osmoles are from urea and 50% from NaCl. The urea contribution is considerably less in infants. It is largely in the collecting ducts where the consequences of CNDI are manifest. Reabsorption of the roughly 10% of filtrate handled by this segment depends on the presence of ADH and the ability of collecting tubules to respond to it. In CNDI, hypothalamic synthesis, posterior pituitary storage, and release of ADH are intact, but end-organ resistance to ADH makes the kidney unable to reabsorb adequate water to maintain electrolyte and fluid balance. Mutational defects in the vasopressin receptor (VR2) on the basolateral membrane of collecting duct principal cells, defects in the translation of information once the receptor is stimulated, or a mutational defect in the apical membrane water channel (AQP2) can lead to impaired ability to reabsorb water. The patient in the case report could lose substantial circulating volume and become severely dehydrated quickly.

Diagnosis

In the presence of dehydration or hypernatremia, urine should be concentrated and low in volume. Polyuria, dilute urine, and mildly low or low-normal serum sodium concentration are suggestive of psychogenic or maternogenic excessive water intake, but polyuria and dilute urine together with high serum sodium concentration and osmolality indicate lack of, or resistance to, ADH. Acquired forms of NDI rarely cause the degree of polyuria and hypernatremia associated with true CNDI.

Once DI is strongly suspected, a careful water deprivation test should be conducted. One approach is summarized in Table 4. A normal response to water restriction or ADH is a urine osmolality ≥450 mOsm/kg water and a urine-to-plasma osmolar ratio of ≥1.5 (usually much more). The response to ADH is blunted in

Table 4. Diagnostic Approach

1. Admit to hospital: severe dehydration can occur during water deprivation without careful monitoring.
2. Make sure the patient is adequately hydrated and has normal electrolytes before starting the test.
3. Start the water restriction after breakfast and after the child voids or wets a fresh diaper.
4. Collect baseline specimens of urine and blood for measurement of electrolytes and osmolality.
5. Weigh every 2 h, follow blood pressure and pulse rate, and do not allow more than 3% to 5% dehydration (weight loss).
6. Check each urine specimen for specific gravity (SG) by using a refractometer because the dipstick is not sufficiently accurate. Also, record osmolality and volume (weigh the diaper if an infant).
7. Check serum electrolytes and osmolality at 4 h and again every 2 h as needed.
8. If urine SG reaches ≥1.015 or osmolality ≥500 mOsm/kg water in an infant or ≥1.020 or osmolality ≥600 mOsm/kg water, stop the test and measure blood electrolytes and osmolality. The patient is not likely to have chronic nephrogenic diabetes insipidus. Although a 6-month-old infant usually can concentrate the urine to ≥1,000 mOsm/kg water, the maximally concentrating ability of an infant a few weeks old is closer to 500 to 550 mOsm/kg water.
9. If serum sodium concentration is ≥150 mEq/L (150 mmol/L) or osmolality is ≥300 mOsm/kg water or if weight decreases by 3% to 5%, stop the test and administer 1-desamino-9-D-arginine vasopressin (dDAVP) after obtaining blood for measurement of electrolytes, osmolality, and plasma antidiuretic hormone.
10. Limit the water deprivation to 8 to 12 h (4 to 6 h in an infant) to avoid dangerous dehydration and allow food at an appropriate time. A standard water deprivation test is 18 h, but not in a patient strongly suspected of having true diabetes insipidus.
11. If polyuria persists with dilute urine, administer intranasal dDAVP or desmopressin acetate in appropriate dose (10 mcg for infants, 20 mcg for older children). Replace urine volume thereafter with an equal amount of water to avoid further dehydration, and check urinary concentration and blood electrolytes and osmolality in 4 h (2 h in infants).
12. If there is uncertainty about nasal absorption of dDAVP, vasopressin can be administered intravenously in a dose 10% of the nasal dose (1 mcg in infants and 2 mcg in older children).

those who have partial DI with a mild phenotype or in psychogenic water drinking, and the response is effectively absent in CNDI (urine osmolality usually does not rise much above 150 to 200 mOsm/kg water).

There are subtle differences between autosomal recessive and dominant forms of CNDI caused by AQP2 mutations. In the recessive form, polyuria and polydipsia are usually present at, or shortly after, birth, and the disease tends to be more severe, with urine osmolality generally not exceeding approximately 200 mOsm/kg water. In the dominant form, the clinical expression tends to become noticeable after 6 to 12 months or even later and may not be as severe (urine osmolality may be higher). There even may be a transient response to ADH.

Treatment

Treatment is designed to provide: 1) sufficient water to maintain normal electrolytes, 2) low renal solute load to minimize water loss, and 3) adequate calories to support growth. Pharmacotherapy usually is needed.

Water

Infants who have CNDI require a constant supply of water, which should be provided every 2 hours, day and night. When able to retrieve and hold a bottle of water, the infant's lifeline remains an available bottle of water. There is essentially no risk in providing excess water because there is no problem diluting the urine. Water intake must replace urine output and insensible loss plus water for growth. When provided, the infant drinks what is needed, as will a child who has ready access to a water faucet. It is critical to realize that affected children need multiple liters of fluid a day. Even infants may need 2 to 3 L or more daily.

Renal Solute Load

Because solutes require urinary water for excretion, the more the kidney concentrates urine (the greater the urinary osmolality), the more osmoles can be excreted in a given volume. If urine concentrates to 1,000 mOsm/kg of water (normal), the kidney can excrete a solute load of 300 mOsm in 300 mL of urine. However, if urine concentrates only to 100 mOsm/kg of water, excreting 300 mOsm requires 3 L of urine. A huge fluid intake is needed to offset such loss. Therefore, formula for infants who have CNDI should contain adequate calories for growth and minimal solute for excretion by the kidney.

The potential renal solute load, as reviewed by Fomon and Ziegler in 1999, (3) refers to solutes–primarily dietary nitrogen and electrolytes– excreted in urine and not incorporated into new tissue or excreted by nonrenal routes. For clinical purposes, re-

nal solute load is composed of urea (from protein), sodium (Na), potassium (K), chloride (Cl), and phosphorus (P). Potential renal solute load in mOsm is quantified by adding the solute load of protein (generally about 4 mOsm/g protein ingested, mostly as urea) to that of Na, K, and Cl in milliequivalents (mEq) and P in mOsm.

The available P is considered to be total P content of milk-based formula and approximately two thirds of soy-based formula because about one third of soy formula P is not absorbed by the bowel. If protein intake is unknown, the clinician can divide the total milligrams of urinary nitrogen by 28 because there are 28 mg of N per millimole (mM) of urea, and most of the urinary N is excreted as urea. The formula is:

Potential renal solute load = urinary N/28 + Na + K + Cl + available P (all in mOsm or mM)

For Na, K, and Cl, the number of mOsm equals the number of mEq, respectively. To convert from mg to mOsm, divide mg of Na by 23, mg of Cl by 35.5, and mg of K by 39. The mOsm content from P can be calculated by dividing the total number of mg by 31. Fomon and Ziegler estimate potential renal solute load to be 93 mOsm/L or 14 mOsm/100 kcal for human milk, 135 mOsm/L or 20 mOsm/100 kcal for milk-based formula, and 160 mOsm/L or 24 mOsm/100 kcal for one soy formula. (3) An estimate for a second soy formula is slightly higher. A potential renal solute load of 20 to 26 mOsm/100 kcal should be safe, although more can be tolerated if enough water is given. The infant who has CNDI needs the lowest renal solute load that supports normal growth and electrolyte balance.

Pharmacotherapy

Several agents in varying combinations may lower urine output, thereby decreasing water needs and facilitating greater caloric intake. Adverse effects of these agents are not common, but must be kept in mind with long-term use of drug therapy (Table 5).

For more than 40 years, thiazides have been known to decrease urine output, paradoxically, in DI. The explanation has been that thiazide decreases Na reabsorption along the distal nephron, leading to additional volume depletion, a decrease in filtration rate, an increase in reabsorption of filtrate along the proximal tubule, and a resultant decreased delivery of filtrate to a defective more distal reabsorptive site. A problem with this explanation is that children who have severe polyuria often are dehydrated with prerenal failure and already should have enhanced this "thiazide-type" response. Nevertheless, they continue to have marked polyuria and progressive dehydration.

Recently, in lithium-induced NDI (a model associated with downregulation of AQP2), thiazide appeared to upregulate both AQP2 and a distal epithelial sodium channel. A similar effect in CNDI could facilitate movement of aquaporin to apical membranes, enhancing the activity of potentially functional water channels. Note that although salt restriction may add to the thiazide effect, stringent salt restriction can cause some children to rebel and receive inadequate caloric intake. A combination of thiazides with amiloride or indomethacin is more effective than thiazide alone in decreasing urine output, but none of these agents reduces urine output to normal, and large quantities of water usually still are needed.

Amiloride, a diuretic that blocks the epithelial Na channel along the cortical collecting tubule, provides additional natriuresis and can offset thiazide-induced hypokalemia through its K-sparing effect. It generally is well tolerated.

Prostaglandins have an inhibitory effect on ADH-stimulated osmotic water permeability of cortical collecting tubules, probably by downregulating AQP2 expression. Indomethacin, a nonspecific cyclo-oxygenase inhibitor, decreases prostaglandin synthesis, attenuates the ADH-inhibiting effect of prostaglandin, and has been used effectively with thiazides to reduce urine output in patients who have NDI. There is evidence that indomethacin increases

Table 5. Dose and Adverse Effects of Commonly Used Drugs

Thiazide

- Hydrochlorothiazide: 1 to 3 mg/kg per day bid
- Hypokalemia
- Hyponatremia
- Alkalosis
- Hypercalcemia
- Hyperglycemia
- Hyperuricemia
- Hepatitis
- Intestinal symptoms
- Bone marrow suppression

Amiloride

- 20 mg/1.73m^2 per day bid–tid
- Hyperkalemia
- Headaches
- Gastrointestinal discomfort

Indomethacin

- 1.5 to 2.5 mg/kg per day tid
- Gastrointestinal discomfort
- Gastrointestinal bleeding
- Headaches
- Renal toxicity
- Hematopoietic adverse effects

the shuttling of AQP2 channels to the apical membrane of collecting ducts. A more specific cyclooxygenase 2 inhibitor, rofecoxib, has been useful in reducing polyuria in patients who have NDI, but has been associated with cardiac ischemia and potentially is renal toxic. Its use in NDI should be curtailed until questions of its safety are settled.

Although CNDI, in contrast to DI, is resistant to ADH, some patients who have CNDI have a mild phenotype or, even if they have significant polyuria and polydipsia, actually respond to ADH. For example, a family having autosomal recessive CNDI was found to have a valine-to-methionine alteration at amino acid #168 in a transmembrane domain of the AQP2 water channel. This mutation caused marked polyuria and thirst in homozygotes, but 1-desamino-9-D-arginine vasopressin (dDAVP), although causing only modest improvement in urine osmolality, resulted in a subjective improvement in polyuria and thirst. In such patients, the mutant water channel may be partly functional and more able to route to its target apical membrane after ADH.

Some patients who have mutant VP2 receptor proteins also show some response to dDAVP. The type of mutation may dictate the severity of disease and the potential for some response to ADH. Therefore, some children who have CNDI may benefit from larger or more frequent doses of dDAVP. A reasonable starting dose is 5 to 30 mcg/d given one to three times daily, titrating to lessen thirst and polyuria.

Newer Considerations

The clarification of intracellular and molecular processes may open the way for more specifically directed therapy. For example, activating cGMP kinase may allow for phosphorylation of AQP2 when cAMP fails to be activated in X-linked disease. Moreover, pharmacologic chaperone molecules may be able to correct the conformation of misfolded proteins retained in the endoplasmic reticulum and help move certain types of potentially functional VR2 or AQP2 mutations to their more appropriate intracellular sites of action. Thus, defining a specific genetic mutational defect eventually may help in the therapy of individual patients.

References

1. Linshaw MA, Stapleton FB, Knapp J. Growth failure—nephrogenic diabetes insipidus. *J Kansas Med Soc*. 1977;78:345–347

2. Hoekstra JA, van Lieburg AF, Monnens LAH, Hulstijn-Dirkmaat GM, Knoers VVAM. Cognitive and psychosocial functioning of patients with congenital nephrogenic diabetes insipidus. *Am J Med Genet*. 1996;61:81–88

3. Fomon SJ, Ziegler EE. Renal solute load and potential renal solute load in infancy. *J Pediatr*. 1999;134:11–14

Suggested Reading

Bichet DG, Oksche A, Rosenthal W. Congenital nephrogenic diabetes insipidus. *J Am Soc Nephrol*. 1997;8:1951–1958

Boccalandro C, de Mattia F, Guo DC, et al. Characterization of an aquaporin-2 water channel gene mutation causing partial nephrogenic diabetes insipidus in a Mexican family: evidence of increased frequency of the mutation in the town of origin. *J Am Soc Nephrol*. 2004;15:1223–1231

Fujiwara TM, Bichet DG. Molecular biology of hereditary diabetes insipidus. *J Am Soc Nephrol*. 2005;16:2836–2846

Linshaw MA. Concentration and dilution of the urine. In: Abman S, ed. *Fetal and Neonatal Physiology*. Philadelphia, Pa: WB Saunders; 2004:1303–1327

Robben JH, Knoers NVAM, Deen PMT. Cell biological aspects of the vasopressin type-2 receptor and aquaporin 2 water channel in nephrogenic diabetes insipidus. *Am J Physiol (Renal Physiol)*. 2006;291:257–270

Sands JM, Bichet DG. Nephrogenic diabetes insipidus. *Ann Internal Med*. 2006;144:186–194

PIR Quiz

Quiz also available online at www.pedsinreview.org.

5. In the first weeks after birth, breastfeeding infants who have congenital nephrogenic diabetes insipidus (CNDI) are *most* likely to present with:

   A. Developmental delay.
   B. Diarrhea.
   C. Hypothermia.
   D. Incessant crying.
   E. Linear growth failure.

6. Diabetes insipidus (DI) is most reliably differentiated from psychogenic excessive water intake (PEWI) by a history of:

   A. Diarrhea in DI.
   B. Hypernatremia.
   C. Pale urine in DI.
   D. Pale urine in PEWI.
   E. Polyphagia in DI.

7. The *most* likely effect to occur during a water deprivation test in a patient who has a complete form of DI is:

   A. Significant decrease in serum osmolality.
   B. Significant decrease in urine osmolality.
   C. Significant increase in serum osmolality.
   D. Significant increase in urine osmolality.
   E. Unchanged serum osmolality.

8. For a patient who has autosomal recessive CNDI, the administration of vasopressin during a water deprivation test will result in:

   A. Significantly higher serum osmolality.
   B. Significantly higher urine osmolality.
   C. Significantly lower serum osmolality.
   D. Significantly lower urine osmolality.
   E. Unchanged urine osmolality.

9. When treating CNDI, in addition to assuring ready access to water and supplying appropriate pharmacotherapy, careful attention to renal solute load and caloric intake is indispensable. The ratio of renal solute load to calories (mOsm/kcal) in a diet that is *most* appropriate for an infant who has CNDI is:

   A. <14 mOsm/100 kcal.
   B. 14 to 26 mOsm/100 kcal.
   C. 27 to 50 mOsm/100 kcal.
   D. 51 to 75 mOsm/100 kcal.
   E. >76 mOsm/100 kcal.

Complementary, Holistic, and Integrative Medicine: Colic

Lawrence D. Rosen, MD,* Cecilia Bukutu, PhD,† Christopher Le,† Larissa Shamseer,† Sunita Vohra, MD, MSc†

Author Disclosure
This article was funded in part by PasseportSanté.net. Dr Vohra is an Alberta Heritage Foundation for Medical Research Population Health Investigator and recipient of a Canadian Institute of Health Research New Investigator Award

Introduction

According to the Wessel criteria, infantile colic is defined as excessive crying for more than 3 hours a day at least 3 days a week for 3 weeks or more in an otherwise healthy baby. (1) As many as 26% of infants are diagnosed with colic, (2) making the condition one of the most common reasons for infant visits to primary care practitioners today. Colic is a self-limiting condition that resolves in approximately 50% of cases at about 3 months of age. (3) Due, in part, to poor understanding of its causes, (2) there is no widely accepted conventional treatment, and families often turn to complementary and alternative medical (CAM) therapies. (4) The largest systematic review to date of treatments for colic found little evidence to support many conventional therapies, while noting that some nutritional- and botanical-based approaches were relatively safe and effective. (5) This review of published scientific literature assesses the efficacy and safety of common CAM therapies in treating infantile colic.

Natural Health Products

Natural health products have been used historically to treat infantile colic, due, in part, to presumed antispasmodic and anti-inflammatory activity. (6)(7) However, few of these products have been assessed in terms of efficacy and safety for use in infants through well-designed clinical trials.

Fennel Seed Oil

The effectiveness of fennel (*Foeniculum vulgare*) seed oil in treating infantile colic was investigated in a randomized controlled trial (RCT) in Russia of 125 colicky infants between the ages of 2 and 12 weeks. (8) Infants were assigned randomly to receive 5 to 20 mL of a 0.1% fennel seed oil emulsion and 0.4% polysorbate-80 or a placebo (0.4% polysorbate-80 in water) up to four times per day for 1 week. Parents recorded symptoms in a diary for 3 weeks that included the week before, the week during, and the week after the trial. The primary outcome measure was a decrease in cumulative crying to fewer than 9 hours per week. At the end of the study, colic symptoms had improved significantly in 40 of 62 (65%) infants from the fennel group compared with 14 of 59 (24%) infants in the placebo group ($P<0.01$). No adverse effects were reported in this study. However, fennel may cause allergic reactions of the skin (rashes) and respiratory tract (asthma and breathing difficulties). Fennel also has been reported to cause seizures. (6) The safety of using fennel long-term is unknown.

Botanical Blends

The efficacy of an herbal tea containing fennel, chamomile, vervain, licorice, and lemon balm to treat colic was investigated in an RCT of 68 Israeli infants ages 2 to 8 weeks. (9) Over a 7-day period, up to a 150-mL dose of herbal tea was offered to infants in the intervention group at the onset of a colic episode up to a maximum of three times a day. The actual average daily intake was two servings per day for a cumulative total of

*Chair, Integrative Pediatrics Council, Old Tappen, NJ.
†Complementary and Alternative Research and Education (CARE) Program, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada. On behalf of the American Academy of Pediatrics Provisional Section on Complementary, Holistic, and Integrative Medicine.

Note: The agents discussed in this series are designated as dietary supplements rather than drugs. Although dietary supplements are regulated by the United States Food and Drug Administration (FDA), their manufacturers may make claims with little evidence and need not prove safety prior to marketing. The burden is on the FDA to monitor safety after the product is on the market. Readers are referred to the 1994 Dietary Supplement Health and Education Act (www.cfsan.fda.gov/~dms/dietsupp.html).

approximately 90 mL/d. The control group received a placebo tea (a mixture of glucose and unspecified natural flavorings) that had the same taste, odor, and appearance as the herbal tea. Parents reported that crying was reduced to fewer than 3 hours daily in 57% of infants in the intervention group compared with 26% in the control group ($P<0.01$). This study did not report on adverse effects of herbal tea consumption and the impact, if any, on infants' nutritional intake. Long-term safety of this herbal combination is unknown.

An Italian RCT examined the efficacy of another herbal preparation in treating breastfed colicky infants ages 21 to 60 days. (10) Each dose consisted of the following standardized extracts: sweet fennel fruit powdered extract (PE) standardized to 0.05% to 0.1% essential oil, chamomile flower PE standardized to 0.3% apigenin, lemon balm essential oil standardized to 2% rosmarinic acid, 0.85 mg of vitamin B_1, 3.24 mg of calcium pantothenate, and 1.20 mg of vitamin B_6. Parents administered 2 mL/kg per day of the herbal preparation twice a day before feeding for 7 days to children in the intervention group (n=41). The control group (n=47) was given a placebo consisting of reverse osmosis-filtered water, fructose, pineapple flavoring, citric acid, and potassium sorbate. Average daily crying time was reduced from about 200 min/d to 76.9 min/d in the treatment group and from about 200 min/d to 169.9 min/d in the placebo group ($P<0.005$). Crying time was significantly reduced in 85% of infants in the intervention group compared with slightly less than 50% of the control group ($P<0.005$). These findings suggest that this standardized herbal preparation relieves infantile colic symptoms. No adverse events were reported in this study; long-term safety is unknown.

Probiotics

Probiotics have been defined as "a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host." (11) These microorganisms colonize the intestinal tracts of infants during the birth process and shortly thereafter. They have been implicated in promoting immunologic balance and digestive health. (12)(13)(14) Savino and associates (15)(16) described quantitative and qualitative differences in probiotic species in colicky versus noncolicky infants.

Most recently, the same research group published results of a trial of *Lactobacillus reuteri* compared with simethicone in the treatment of infantile colic. (17) In this trial, 90 exclusively breastfed colicky infants between 21 and 90 days of age were randomized to either probiotic *L reuteri* (10^8 live bacteria per day) or simethicone (60 mg/d) for 28 days. Mothers were instructed to avoid all sources of cow milk during the trial. At the start of the study, both groups of infants reportedly cried for approximately 200 min/d. The probiotic treatment group had a significantly reduced crying time by only 7 days into the trial (159 min/d versus 177 min/d in the simethicone group), a disparity that widened at weeks 2, 3, and 4 (51 min/d versus 145 min/d). At the endpoint of the study, 95% of the probiotic treatment group were considered "responders" (ie, no longer met Wessel criteria) compared with only 7% of the simethicone group. No significant adverse effects were reported.

The use of probiotics in healthy individuals generally is safe, but incidents of bacteremia/septicemia, pneumonia, and meningitis have been documented in immunocompromised and severely debilitated patients. (18)(19)(20)(21)(22) Similar adverse events were documented in two pediatric case reports in which *Lactobacillus GG* (10 billion colony-forming units/d) caused bacteremia. (20) Probiotic use should be discussed with the child's physician because probiotic safety is relative rather than absolute.

Nutritional Modulation

Nutritional modulation is one of the few potentially preventive and therapeutic options for infants who have colic. It does not appear that breastfeeding exclusively prevents colic, (23) but it has been observed that certain foods (eg, cruciferous vegetables, chocolate) ingested by breastfeeding mothers may lead to excessive infant irritability. (24)(25) Although there is no clear consensus on avoidance of these foods for allergy prevention, (26) Hill and colleagues (27) demonstrated via an RCT that exclusion of certain allergenic foods (cow milk, soy, wheat, eggs, peanuts, tree nuts, and fish) was positively associated with a reduction in colic in breastfed infants. In their investigation, 107 infants (mean age, 5.7 weeks) presenting with excessive irritability (average crying time more than 300 min/d) were randomized to a 1-week trial of maternal low-allergen diet versus control (noneliminination) diet. At the completion of the trial, 74% of treated infants were crying/fussing less frequently compared with 37% of the control group.

Whey hydrolyzed formula (hypoallergenic formula) has been shown in a small RCT to be more effective than nonhydrolyzed cow milk formulas in reducing crying times in colicky babies (Table 1). (28) A 2000 report from the American Academy of Pediatrics Committee on

Table 1. **Summary of Nutritional Interventions**

Authors	Study Type	Population	Intervention	Control	Outcome	Adverse Effects
Lucassen (28)	Randomized, double-blind, parallel trial	43 healthy, formula-fed infants ages younger than 24 wk	Hypoallergenic whey hydrolysate formula milk	Standard cow milk formula	Decreased duration of crying by 63 min/d	None reported
Forsythe (33)	Randomized double-blind, multiple crossover trial	17 infants ages younger than 8 wk	Hypoallergenic casein hydrolysate formula milk	Standard cow milk formula	No notable difference in incidence of colic between groups	None reported
Hill et al. (32)	Randomized double-blind, placebo-controlled trial	115 infants ages 4 to 16 wk	Hypoallergenic casein hydrolysate formula milk	Modified cow milk formula	Number of bottle-fed infants too small to determine effect on the bottle-fed subgroup	None reported
Campbell (34)	Randomized, double-blind, placebo-controlled crossover trial	19 infants ages 3 to 14 wk	Soy formula milk	Standard milk formula	Duration of colic symptoms significantly reduced with soy milk ($P<0.01$)	None reported
Evans et al. (35)	Double-blind, placebo-controlled crossover trial	20 exclusively breast-fed infants ages 3 to 18 wk, who had persistent colic	Soy formula milk consumed by the breastfeeding mother	Cow milk consumed by the breastfeeding mother	No beneficial effects on the incidence of colic	None reported
Lothe et al. (36)	Double-blind crossover study	60 infants ages 2 to 12 wk	Soy formula milk	Cow milk formula	Colic symptoms disappeared in 11 infants (18%) 48 h after receiving soy formula but not after receiving cow milk formula. In 32 infants (53%), the symptoms were unchanged on soy and cow milk formula.	Eight infants had adverse reactions caused by other types of food, two had a severe form of multiple food intolerance, and two reacted to soy oil

Nutrition recommended the use of hypoallergenic formula for infants who have allergies and a trial of hypoallergenic formula for severe colic. (29) A cost-benefit analysis of hypoallergenic-labeled infant formulas is needed because they cost up to three times more than standard formulas. (29)

Evidence is insufficient to support the use of casein hydrolyzed formula, soy, or partially hydrolyzed formulas as therapies for colic (Table 1). (29)(30)(31)(32)(33)(34)(35)(36) Soy infant formula has a high phytoestrogen content, which may pose a risk to future fertility and sexual development. (37) Because of this effect, the Chief Medical Officer in England has recommended that soy infant milk formula not be the first choice for treatment of infants who have lactose intolerance or cow milk sensitivity. (38)

A small Norwegian crossover RCT examined the analgesic effect of sucrose on infant colic (n=19). (39) Parents gave infants 2 mL of 12% sucrose solution (intervention) or 2 mL of distilled water (control) after persistent crying and failed attempts to console the infant. Parents reported that symptoms improved in 63% of the infants given sucrose and in only one child (5%) given placebo ($P<0.01$). In this study, the observed benefit of

Table 2. **Summary of Chiropractic Interventions**

Authors	Study Type	Population	Intervention	Control	Outcome	Adverse Effects
Wiberg et al. (45)	Randomized controlled trial	50 infants ages 2 to 10 wk	Spinal manipulative therapy applied with light finger tips	Infants given the drug dimethicone	At days 8 to 11, crying reduced by 2.7 h in treated group compared with 1 h in control group (P=0.004)	Symptoms reported to have worsened in four infants from the dimethicone group
Olafsdottir et al. (46)	Randomized controlled trial	86 infants ages 3 to 9 wk	Spinal manipulative therapy applied with light finger tips	Infants held for 10 min by the nurse	No improvement	None reported
Mercer et al. (44)	Pilot randomized controlled trial	30 infants ages 0 to 8 wk	Spinal manipulative therapy	Treated with a nonfunctional detuned ultrasonography machine	Colic symptoms resolved in 93% of infants who had received up to six treatments during 2 wk	None reported

sucrose seems to have been short-lived (<30 min), which may indicate that it is not a practical treatment. (5) Although no adverse effects were reported, those considering using sucrose should not substitute honey because unpasteurized honey may cause botulism in infants. (40)

Manipulative Therapies

Chiropractic

The World Federation of Chiropractic defines chiropractic as "a health profession concerned with the diagnosis, treatment, and prevention of mechanical disorders of the musculoskeletal system, and the effects of these disorders on the function of the nervous system and general health." (41) Chiropractic manual treatments include vertebral adjustment and other joint and soft-tissue manipulation. Very few reliable data are available regarding the safety of using spinal manipulation in pediatric populations. (42) The Canadian Coordinating Office for Health Technology Assessment assessed the sum of evidence on spinal manipulative therapy (SMT) in the treatment of infantile colic in a systematic review of three randomized controlled trials. (43) These three trials were believed to suffer from significant methodologic flaws. Two (44)(45) of the trials reported SMT to be effective in treating colic, but the third and largest study (46) found it to be of no benefit (Table 2). At this point, it is not possible to conclude that chiropractic care is an effective treatment for colic. More RCTs are needed to determine the safety and efficacy of chiropractic adjustments in treating colic.

Osteopathy

The World Osteopathy Health Organization defines osteopathy as a "system of healthcare which relies on manual contact for diagnosis and treatment." (47) It emphasizes the structural and functional integrity of the body and the body's intrinsic tendency for self-healing. One United Kingdom study has investigated the efficacy of osteopathic treatment for infantile colic. (48) In this open, controlled, prospective study, 28 colicky infants were randomized to receive either individualized cranial osteopathic manipulation by the same osteopath once weekly for 4 weeks or to receive no treatment (control). Time spent crying, sleeping, and being held or rocked was recorded in a parent-completed diary. Children in the osteopathic group had reduced crying (63% compared with 23% for controls) and improved sleeping (11% compared with 2% for controls). Children in the intervention group also required less holding/rocking. No adverse events were reported. These findings suggest that cranial osteopathic treatment benefits some infants who have colic. Confirmatory, larger clinical trials and cost-benefit analyses are needed before general public policy recommendations about osteopathic treatment for colic can be made.

Massage

A Finnish RCT compared the effectiveness of infant massage (n=28) with the use of a crib vibrator (n=30) in treating colicky infants younger than 7 weeks of age over a 4-week period. (49) The massage group of infants received parent-administered gentle stroking of the skin over the head, body, and limbs using olive oil and maintaining eye contact three times per day. The crib vibrator was used for 25-minute periods three times daily on the control group. At the end of the study, parents reported similar reductions in total crying: a mean decrease of 48% in the massage group and 47% in the vibrator group. A 2006 Cochrane Database Systematic Review of the effectiveness of infant massage in promoting physical and mental health in infants concluded that there is evidence of benefits on mother-infant interaction, infant sleeping, and crying but noted that more rigorous RCTs are needed before infant massage can be recommended routinely for treating colic. (50)

Education and Behavioral Interventions

Parent education and behavioral management have been evaluated for treatment of infantile colic. Keefe and associates (51) demonstrated in an RCT of 121 term infants (2 to 6 weeks old) that a 4-week home-based behavioral intervention was more effective than routine care in reducing parenting stress. The treatment group cried, on average, for 1.7 hours less per day than the control group ($P=0.02$). Dihigo (52) evaluated behavior modification in treating colicky infants. Twenty-three infants were assigned randomly to intervention, nonintervention, and control groups. Crying diaries kept by the parents were used to obtain quantitative measurements of crying before and after intervention. Among infants whose parents received individualized counseling and education interventions, crying was reduced significantly from nearly 4 hours to slightly more than 1 hour per child ($P<0.05$). Parkin and colleagues (53) found no significant difference in average daily hours of crying in a 2-week RCT comparing three interventions for colic (reassuring mothers, providing mothers with focused counseling, and giving infants car ride simulation) in 38 mother-infant pairs (mean infant age, 6.8 wk).

Conclusion

Evidence from small, often pilot studies indicates potential benefit in integrating specific CAM therapies to treat infantile colic. Specific therapies that have promise include some natural health products, nutritional modulation, cranial osteopathy, infant massage, and parental behavioral training. Questions remain regarding both the safety and efficacy of these therapies for the treatment of infantile colic. Larger confirmatory trials are needed to assess safety and cost-effectiveness before routine use of these therapies for colic can be recommended.

To view references for this article, visit pedsinreview.org and click on this article title.

Clarification

In the Complementary, Holistic, and Integrative Medicine: Butterbur article that appeared in the June 2007 issue of *Pediatrics in Review*, review of a study that examined the effects of butterbur treatment in asthma on page 235 states that 50 g of butterbur extract was administered three times daily. That dose was incorrect. The correct dose is 50 mg.

Massage

A Finnish RCT compared the effectiveness of infant massage (n=28) with the use of a crib vibrator (n=30) in treating colicky infants younger than 7 weeks of age over a 4-week period. (49) The massage group of infants received parent-administered gentle stroking of the skin over the head, body, and limbs using olive oil and maintaining eye contact three times per day. The crib vibrator was used for 25-minute periods three times daily on the control group. At the end of the study, parents reported similar reductions in total crying: a mean decrease of 48% in the massage group and 47% in the vibrator group. A 2006 Cochrane Database Systematic Review of the effectiveness of infant massage in promoting physical and mental health in infants concluded that there is evidence of benefits on mother-infant interaction, infant sleeping, and crying but noted that more rigorous RCTs are needed before infant massage can be recommended routinely for treating colic. (50)

Education and Behavioral Interventions

Parent education and behavioral management have been evaluated for treatment of infantile colic. Keefe and associates (51) demonstrated in an RCT of 121 term infants (2 to 6 weeks old) that a 4-week home-based behavioral intervention was more effective than routine care in reducing parenting stress. The treatment group cried, on average, for 1.7 hours less per day than the control group ($P=0.02$). Dihigo (52) evaluated behavior modification in treating colicky infants. Twenty-three infants were assigned randomly to intervention, nonintervention, and control groups. Crying diaries kept by the parents were used to obtain quantitative measurements of crying before and after intervention. Among infants whose parents received individualized counseling and education interventions, crying was reduced significantly from nearly 4 hours to slightly more than 1 hour per child ($P<0.05$). Parkin and colleagues (53) found no significant difference in average daily hours of crying in a 2-week RCT comparing three interventions for colic (reassuring mothers, providing mothers with focused counseling, and giving infants car ride simulation) in 38 mother-infant pairs (mean infant age, 6.8 wk).

Conclusion

Evidence from small, often pilot studies indicates potential benefit in integrating specific CAM therapies to treat infantile colic. Specific therapies that have promise include some natural health products, nutritional modulation, cranial osteopathy, infant massage, and parental behavioral training. Questions remain regarding both the safety and efficacy of these therapies for the treatment of infantile colic. Larger confirmatory trials are needed to assess safety and cost-effectiveness before routine use of these therapies for colic can be recommended.

To view references for this article, visit pedsinreview.org and click on this article title.

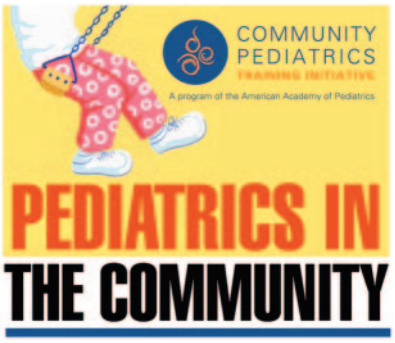
Clarification

In the Complementary, Holistic, and Integrative Medicine: Butterbur article that appeared in the June 2007 issue of *Pediatrics in Review*, review of a study that examined the effects of butterbur treatment in asthma on page 235 states that 50 g of butterbur extract was administered three times daily. That dose was incorrect. The correct dose is 50 mg.

Pediatrics in the Community: Cap4Kids.org: Connecting Pediatricians to the Community at the Speed of Light

Daniel R. Taylor and C. Andrew Aligne

Pediatr. Rev. 2007;28;386-387
DOI: 10.1542/pir.28-10-386



Author Disclosure
Drs Taylor and Aligne did not disclose any financial relationships relevant to this article.

Cap4Kids.org: Connecting Pediatricians to the Community at the Speed of Light

The Children's Advocacy Project of Philadelphia (Cap4Kids) was developed in 2004 to help busy practitioners learn more about social service agencies, advocacy programs, and laws in their geographic area.

The project was started by pediatric residents Raj Raman and, subsequently, Payal Maniar at St. Christopher's Hospital for Children, with attending oversight by Dan Taylor, director of the residency advocacy program. They realized that most physicians were not aware of the myriad social service agencies in their area and, therefore, compiled a comprehensive, verified, up-to-date list of relevant organizations in Philadelphia. This process was extremely time-consuming, but it uncovered many programs and individuals who are committed to improving the lives of children.

The project was funded initially by a grant from the St. Christopher's Foundation for Children and received technical assistance from the Drexel University College of Media Arts and Design to design a web site (www.cap4kids.org) to disseminate the content that had been compiled. In addition to connecting practitioners with service agencies, Cap4Kids provided up-to-date parent handouts and an advocacy teaching tool for residents and students.

After testing the website, the residents introduced it to as many practitioners as possible. To date, they have personally presented this project to all of the medical staff and residents at St. Christopher's Hospital for Children, Children's Hospital of Philadelphia, Jefferson University Medical Center, Einstein Hospital, and duPont Children's Hospital. They also have presented this project to the City of Philadelphia's Director of Maternal and Family Services, all WIC employees, and the Wireless Philadelphia. Also, with the support of the Pennsylvania Chapter of The American Academy of Pediatrics, they e-mailed announcements to all pediatricians in Pennsylvania.

The initial success of this project can be measured in several ways. Almost 1,000 health professionals, educators, parents, and concerned citizens signed up for the Cap4Kids listserve. The website has had more than 1,000,000 hits—about 2,000 a day. Cap4Kids has been featured in national medical journals as well as in the local newspapers, radio, and television. The following communities have replicated Cap4Kids: the State of Hawaii (Kapi'olani Medical Center), New York City (Mount Sinai), St. Louis (Children's Hospital of St. Louis), Pittsburgh (Children's Hospital of Pittsburgh), Central Susquehanna Valley (Geisinger Medical Center), and Baltimore (Johns Hopkins University).

Comments from users of Cap4Kids show how valuable this resource has been for practitioners in Philadelphia:

"A wonderful site! Has truly helped my patients tremendously. Has made me a much more effective and complete pediatrician."

"This is a wonderful resource for

people who don't easily have access to a social worker to help them find the community resources they need for themselves or their clients."

Daniel R. Taylor, DO
Assistant Professor
Drexel University College of Medicine
Director, Community Pediatrics and Child Advocacy
St. Christopher's Hospital for Children
Philadelphia, Pa.

SECTION EDITOR'S NOTE. These residents helped children across the country because they lowered barriers separating pediatricians from community agencies. Building and publicizing Cap4Kids.org was much more effective than simply exhorting doctors to use community resources. Their success illustrates the general finding from public health research that one of the best ways to change behaviors is to make the desired behavior as pleasant, productive, and pervasive as possible. (1)

Readers are urged to visit www.cap4Kids.org to explore the types of resources to which the site directs the interested visitor.

C. Andrew Aligne, MD
Co-Director of the Pediatric Links to the Community Program
University of Rochester School of Medicine and Dentistry
Rochester, NY

If interested in submitting a story of a resident community project, please contact the Section Editor: C. Andrew Aligne, MD, MPH, Co-Director of the PLC Program, Department of Pediatrics, University of Rochester School of Medicine, 601 Elmwood Avenue, Box 777. Rochester, NY 14642. Andrew_Aligne@urmc.rochester.edu

Reference

1. Farley TA, Cohen DA. *Prescription for a Healthy Nation*. Boston, Mass: Beacon Press; 2005

Pediatrics in the Community: Cap4Kids.org: Connecting Pediatricians to the Community at the Speed of Light

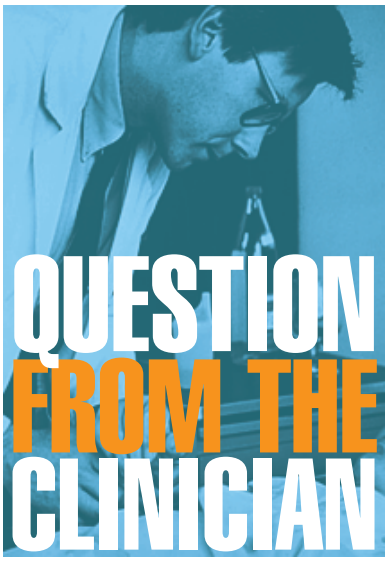
Daniel R. Taylor and C. Andrew Aligne

Pediatr. Rev. 2007;28;386-387
DOI: 10.1542/pir.28-10-386

Question From the Clinician: Alternating Acetaminophen and Ibuprofen in the Treatment of Fever

Kami Jow and Janet R. Serwint

Pediatr. Rev. 2007;28;395
DOI: 10.1542/pir.28-10-395



Alternating Acetaminophen and Ibuprofen in the Treatment of Fever

Question

Is there any benefit, theoretically or clinically, to alternating acetaminophen and ibuprofen in the treatment of fever?

Kami Jow, MD

Answer

Counseling parents to alternate acetaminophen and ibuprofen has become a more common practice among pediatricians. Mayoral and associates (1) found that the single reason given most frequently by pediatricians who adopted this practice was that they thought this was recommended by the American Academy of Pediatrics, even though no such recommendation exists. Only one randomized, controlled trial has evaluated alternating acetaminophen and ibuprofen. (2) Findings of the study, which was conducted in Israel, suggested that the alternating regimen was more effective in reducing fever, but potential problems with this study should be considered in interpreting the results. Patients were given a larger loading dose of an antipyretic at the beginning of the study, which is not the standard of care in other countries such as the United States. Also, the alternating group used fewer doses as early as the first 24 hours, which could be a reflection of the impact of the loading dose or more self-limited causes for the fever.

Although a child's comfort is always important to consider, alternating acetaminophen and ibuprofen can lead to drug errors as to which medication to use next in the sequence, resulting in potential toxicities such as hematemesis, hepatoxicity, and renal failure in a dehydrated patient. (3) Single regimens, either acetaminophen or ibuprofen, should provide adequate treatment for the child who is uncomfortable due to fever. Perhaps most importantly, alternating antipyretics reinforces fever phobia that fever should be reduced at all costs rather than supporting the concept that fever may serve a potential benefit in fighting infection. (4)

Janet R. Serwint, MD
Consulting Editor

References

1. Mayoral CE, Marino RV, Rosenfeld W, Greensher J. Alternating antipyretics: is this an alternative? *Pediatrics.* 2000;105:1009–1012

2. Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double blind study. *Arch Pediatr Adolesc Med.* 2006;160:197–202

3. Saphyakhajon P, Greene G. Alternating acetaminophen and ibuprofen in children may cause parental confusion and is dangerous. *Arch Pediatr Adolesc Med.* 2006;160:757

4. Schmitt BD. Concerns over alternating acetaminophen and ibuprofen for fever. *Arch Pediatr Adolesc Med.* 2006;160:757

Question From the Clinician: Alternating Acetaminophen and Ibuprofen in the Treatment of Fever

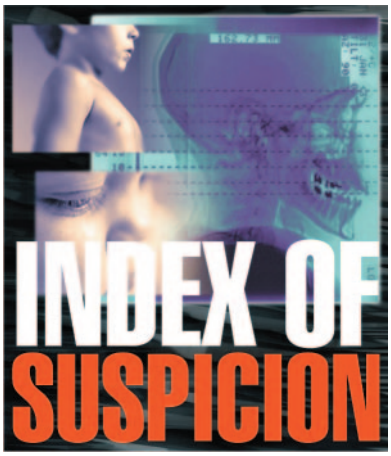
Kami Jow and Janet R. Serwint

Pediatr. Rev. 2007;28;395
DOI: 10.1542/pir.28-10-395

Index of Suspicion

Russell Hopp, Nagendra Natarajan, Mary L. Lewis, Karthik Krishnan and Warees T. Muhammad

Pediatr. Rev. 2007;28;389-394
DOI: 10.1542/pir.28-10-389



The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting Dr. Nazarian at LFredN@aol.com.

Author Disclosure

Drs Hopp, Natarajan, Lewis, Krishnan, Muhammad, and Logan did not disclose any financial relationships relevant to these cases.

Frequently Used Abbreviations

ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BUN:	blood urea nitrogen
CBC:	complete blood count
CNS:	central nervous system
CSF:	cerebrospinal fluid
CT:	computed tomography
ECG:	electrocardiography
ED:	emergency department
EEG:	electroencephalography
ESR:	erythrocyte sedimentation rate
GI:	gastrointestinal
GU:	genitourinary
Hct:	hematocrit
Hgb:	hemoglobin
MRI:	magnetic resonance imaging
WBC:	white blood cell

Case 1 Presentation

A 10-month-old Caucasian boy is referred to the GI clinic because of a 3-month history of recurrent vomiting, abdominal pain, and weight loss, for which he has been hospitalized twice. The vomiting has occurred two to three times per week, is nonprojectile and nonbilious, and has no relation to eating. The abdominal pain has been crampy, occurs primarily in the daytime, and does not correlate with eating or stooling. No specific location for the pain has been identified. The infant has lost 5 lb over the last 3 months.

His daily diet includes 6 to 8 oz of milk, 16 to 24 oz of juice, 16 to 24 oz of water, and table foods, including beef. His stools have been normal, he has slept well, and there is no family history of similar disorders.

Previous studies have included CBC, comprehensive metabolic panel, hantavirus immunoglobulin G and M (IgA/IgM) titers, urinalysis, stool cultures, and testing for *Clostridium difficile* toxin A and B and the antigens of rotavirus, *Giardia,* and *Cryptosporidium*. All results have been normal or negative.

On examination, the child is at the 5th percentile for weight, 4th percentile for height, and 16th percentile for head circumference. All other findings are normal. The following studies yield normal results: iron, amylase and lipase, C-reactive protein, ESR, thyroglobulin-stimulating hormone, free thyroxine, serum IgA, and upper GI radiographic series. Tissue transglutaminase and gliadin antibody IgG and IgA concentrations are normal. He has an Hgb value of 13 g/dL (130 g/L), Hct of 37% (0.37), platelet count of 305×10^3/mcL (305×10^9/L), and WBC count of 9.62×10^3/mcL (9.62×10^9/L) (36% neutrophils, 44% lymphocytes, 5% monocytes, 15% eosinophils). One additional study reveals the diagnosis.

Case 2 Presentation

A 12-year-old girl who was treated at 18 months of age for medulloblastoma presents with 2 weeks of polyuria and polydipsia, accompanied by constipation and intermittent abdominal pain. She reports no weight loss, vomiting, diarrhea, anorexia, or polyphagia, nor does she complain of headache, visual disturbance, seizures, motor or sensory disturbance, hematuria, or flank pain.

Her medulloblastoma was resected completely at the time of diagnosis and a ventriculoperitoneal shunt placed to relieve hydrocephalus. After rigorous chemotherapy, she was believed to be in remission. She is developmentally normal and has led an active life.

On examination, the girl is interactive and in no distress. Vital signs and physical findings are normal except for a soft, nontender, mobile mass in the left lower quadrant of her abdomen. Findings on urinalysis are normal. Her serum electrolyte values are normal except for a calcium concentration of 17.9 mg/dL (17.9 mmol/L) (normal, 8.2 to 10.7 mg/dL [8.2 to 10.7 mmol/L]). Her ionized calcium concentration is 8.2 mg/dL (8.2 mmol/L) (normal, 4.5 to 5.3 mg/dL [4.5 to 5.3 mmol/L]) and her phosphorus concentration is 2.2 mg/dL (2.2 mmol/L) (normal, 2.6 to 5.0 mg/dL [2.6 to 5.0 mmol/L]). Results of a CT scan and MRI of the head are normal. Subsequent testing establishes the cause of her condition.

Case 3 Presentation

A 4-year-old boy is evaluated for respiratory distress. He has had chronic

stridor and has been diagnosed as having reactive airway disease. Two months ago, he was treated in an ED for stridor and chest retractions with levalbuterol and fluticasone by inhalation as well as cefdinir. The following week, he was hospitalized for an exacerbation of his respiratory distress and was reported to have a lesser degree of stridor at the time of discharge. One week later, he experienced another exacerbation.

At a hospital today, he is experiencing persistent biphasic stridor and chest retractions despite therapy with albuterol nebulization; he requires oxygen at 1 L/min to maintain an oxygen saturation level above 90%. A chest radiograph is clear. The patient is transferred to a children's hospital.

On physical examination, the boy is in respiratory distress but alert and has a temperature of 98°F (36.7°C), pulse of 142 beats/min, respiratory rate of 36 breaths/min, and oxygen saturation of 91% in room air. He has biphasic stridor, retractions, and wheezing. No chest wall deformity is noted. Oropharyngeal, cardiac, abdominal, and neurologic findings are normal.

The patient has a low-pitched voice, which was noted initially when his chronic wheezing began. An additional procedure reveals the cause of his respiratory distress.

Case 1 Discussion

The differential diagnosis of this infant's condition included GI reflux disease (GERD), celiac disease, chronic infection, endocrine disorders, and eosinophilic gastroenteropathy. Although his diet was poorly balanced, that factor was not believed to be responsible for his clinical picture. The only positive laboratory finding was peripheral eosinophilia. The patient initially was discharged from the hospital with dietary advice and was given lansoprazole 15 mg at bedtime. Upper GI endoscopy was scheduled. Symptoms continued while he was on the medication.

Endoscopy revealed whitish material on the esophageal mucosa, with mild friability but no ulceration. The gastroesophageal junction appeared normal. The stomach had no ulceration, erythema, nodularity, or friability. The pylorus and duodenum appeared normal. Biopsies were taken from the esophagus, stomach, and duodenum.

Histologic examination showed severe hyperplasia of the esophageal basal cell layer, extension of the vascular papillae, and a marked eosinophilic infiltrate with microabscess formation (maximum eosinophil count 46 cells/high-power field [hpf]). No acute inflammation or microorganisms were noted. The underlying lamina propria showed chronic lymphoplasmacytic cell infiltrate, edema, and scattered eosinophils. These findings suggested an allergic process, specifically eosinophilic esophagitis (EE). Food allergy skin testing was strongly positive for beef (3+) and pork (4+).

The Condition

Virtually unknown prior to the early 1990s, EE is being identified increasingly in gastroenterology and allergy/immunology practices. Primary EE, described as inflammation of the esophagus with eosinophilic infiltration, also is called idiopathic EE or allergic esophagitis. EE is considered an atopic disease closely related to asthma, allergic rhinitis, and eczema. Although the incidence of EE is increasing in the pediatric population, often it is misdiagnosed as recalcitrant reflux esophagitis. EE is more common in males, and the mean age of onset is 10.5±5.4 years.

The symptoms of EE vary with age and often mimic GERD. The key clinical clue is the presence of signs and symptoms that do not improve with traditional GERD therapy, with or without a history of asthma or allergy. EE can present with abdominal pain, chest pain, choking, diarrhea, dysphagia, recurrent food impaction, failure to thrive, nausea, vomiting, and weight loss. Predominant symptoms of EE in adults, older children, and adolescents are dysphagia and food impaction. In younger children and infants, manifestations are vague, most commonly vomiting and abdominal pain.

EE is diagnosed definitively only on biopsy. Endoscopic studies may show findings that include narrowing, furrowing, mucosal rings, ulcerations, whitish papules, and polyps (Figure). Microscopy reveals that the lesions are caused by infiltration of the epithelium by eosinophilis, a process that often forms microabscesses that appear endoscopically as pinpoint white exudates. The number of mucosal eosinophils helps to make the diagnosis and differentiate EE from GERD. On biopsy, up to 7 eosinophils/hpf is strongly indicative of GERD, 7 to 24 eosinophils/hpf is suggestive of a combination of GERD and food allergy or EE, and more than 24 eosinophils/hpf is diagnostic of EE. The eosinophilic infiltration can involve both the proximal and distal esophagus. Once EE is diagnosed, additional evaluation for food or aeroallergen sensitization by skin testing or radioallergosorbent testing (RAST) should be undertaken.

Pathophysiology

EE is an allergic disease of the esophagus, often involving food or aeroallergen sensitivity. Normally, there are no eosinophils in the esophageal mucosa. Several factors work to-

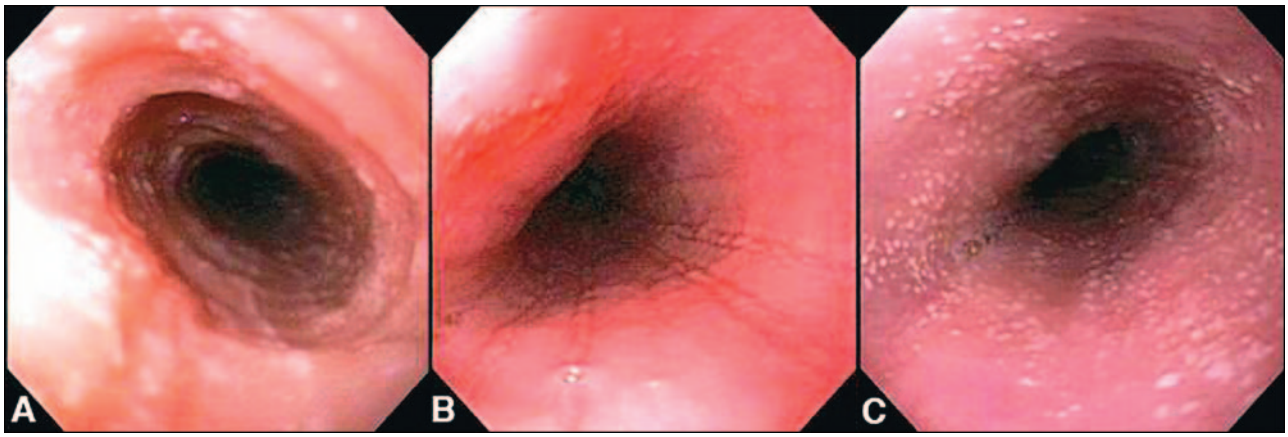


Figure. Endoscopy showing (A) rings, (B) furrows, and (C) exudates in patients who have eosinophilic esophagitis. Courtesy of Doernbecher Children's Hospital.

gether to attract eosinophils to the esophagus, thus causing the clinical symptoms and endoscopically observable changes. Inflammatory mediators are involved in the accumulation of eosinophils in tissue. These mediators include interleukin-1 (IL-1), IL-3, IL-4, IL-5, IL-13; granulocyte-macrophage colony-stimulating factor; chemokines RANTES ("regulated on activation normal T cell expressed and secreted"); monocyte chemotactic protein-3 and -4; macrophage inflammatory protein-1 alpha; and eotaxin-1, -2, and -3. Recent studies have identified eotaxin-1 as a key inflammatory mediator involved in the accumulation of eosinophils in the GI tract. Eotaxin is a chemokine expressed by the intestinal tissue (not the esophagus) that selectively attracts eosinophils. Eotaxin usually regulates the baseline number of eosinophils in tissues, and in EE, eotaxin-1 is overexpressed after food or aeroallergen sensitization.

In the target tissue, eosinophils have cytotoxic effects on the epithelium, causing the changes seen in EE. The eosinophil granule contains several chemicals that eventually cause the damage. The eosinophil granule is composed of major basic protein-1 and -2, eosinophilic cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase. Charcot-Leyden crystals, which are the remains of eosinophil degranulation, can be seen on microscopic examination in patients who have EE.

Therapy And Follow-up

Treatments include lifestyle changes such as elimination of specific food or aeroallergens, use of steroids (systemic or topical), leukotriene receptor modifiers, and proton pump inhibitors. Whether to use single therapy or a combination depends on the patient's profile. A trial of specific food antigen or aeroallergen elimination always should be considered initially in the treatment of EE.

If symptoms persist or it is difficult to eliminate the allergen completely, a trial of steroids should be considered. Systemic steroids are used for acute exacerbations; topical steroids are used for maintenance. When using topical steroids, the patient is instructed to swallow a dose from a metered-dose inhaler without a spacer, which promotes deposition of steroid on the esophageal mucosa. Topically inhaled fluticasone decreases the toxicity of steroid use because this drug undergoes first-pass liver metabolism after minimal GI absorption. Leukotriene receptor modifiers and proton pump inhibitors have been used in treating EE and improve symptoms without resolving the mucosal eosinophilia.

Monitoring of clinical symptoms and routine surveillance of the GI tract with endoscopy are the primary follow-up options. If a patient is avoiding a specific food allergen, such as beef and pork, the decision to reintroduce the food is a topic of debate. When the allergenic food is reintroduced, rebiopsy often is performed.

At present, it is difficult to answer specific questions about duration of therapy, reintroduction of foods, and long-term effects of the disease. It is not certain if the disease remits, as does eczema, or lasts into the adult years, as does allergic rhinitis. The disease is followed best with the collaboration of allergy and gastroenterology specialists.

Lessons for the Clinician

EE should be in the differential diagnosis of any pediatric patient who presents with recurrent vomiting, diarrhea, failure to thrive, dysphagia, abdominal pain, or food impaction. EE should be suspected in any pa-

tient who manifests treatment failure for GERD. Evaluation includes an allergy history, CBC looking for eosinophilia, endoscopy, and skin prick or RAST testing looking for food or aeroallergen sensitization. Treatments include elimination of allergens, systemic or topical steroids, leukotriene receptor modifiers, and proton pump inhibitors, individualized to the patient. Once treatment is initiated, follow-up biopsies should be performed to evaluate efficacy. (*Russell Hopp, DO, Nagendra Natarajan, MD, Creighton University, Omaha, NE*)

EDITOR'S COMMENT. Eosinophilic-associated intestinal diseases have been diagnosed more often in children in the past 10 years. Although EE is the most common, any level of the GI tract can be involved. The diagnosis and treatment in children requires the coordination of primary care pediatricians and specialists. Endoscopy is required for diagnosis, along with proper pathologic confirmation. The pathophysiology of these diseases overlaps with that of asthma, allergic rhinitis, and atopic dermatitis. Most children have concomitant allergic disease, and many have associated food allergies. It is amazing that a "new" allergic disease can develop after hundreds of years of our being aware of asthma.—LFN

Case 2 Discussion

The girl's severe hypercalcemia did not respond to hydration and treatment with a loop diuretic. Because she had a low serum phosphorus concentration and no evidence for recurrence of her medulloblastoma, the initial diagnosis was primary hyperparathyroidism. However, her serum parathyroid hormone (PTH) concentration was less than 1 pg/mL (0.1053 ng/L), appropriately suppressed for her hypercalcemic state. Her plasma parathyroid hormone-related peptide (PTHrP) concentration was 4.4 pmol/mL. Often, no PTHrP is detectable in the blood, although healthy individuals can have a value that is measurable but less than 1.3 pmol/mL. Renal ultrasonography showed an extensive pelvic mass with heterogeneous echogenicity without nephrocalcinosis or nephrolithiasis. Abdominal/pelvic CT scan confirmed that an 11×12×11.5-cm heterogeneous mass occupied the pelvis and displaced the bladder. After complete resection, small cell ovarian tumor was diagnosed histologically, representing a second primary malignancy in the child. Postoperatively, the serum calcium and PTHrP concentrations returned to normal, confirming that the tumor was secreting PTHrP.

The Physiologic Abnormality

True hypercalcemia is an elevation of the free or ionized serum calcium concentration. Hypercalcemia occurs when calcium absorption from the intestine or reabsorption from bone exceeds calcium excretion into the urine or deposition in bone. Patients often are asymptomatic or exhibit nonspecific symptoms. Any signs or symptoms may stem from the elevated serum calcium concentration itself or from the underlying pathologic process. Typically, the severity of symptoms corresponds with the degree of hypercalcemia and may include neurologic manifestations such as headache, vomiting, and altered mental status; cardiac abnormalities, including arrhythmias, decreased QT interval, and hypertension; GI symptoms such as stomach or intestinal dysfunction, constipation, and abdominal pain; and renal abnormalities, including polydipsia, polyuria, dehydration, and nephrolithiasis.

Differential Diagnosis

Hypercalcemia can be produced by a variety of disorders, necessitating a systematic approach to its diagnosis. A single elevated serum calcium concentration should be confirmed. An ionized calcium value also should be checked to exclude the effect of albumin on the measured concentration of calcium. If the ionized calcium is elevated, initial clues to the cause of hypercalcemia are found in two routine laboratory evaluations: the serum phosphorus concentration and the ratio of calcium to creatinine in the urine.

If the urine calcium/creatinine ratio is low, two possibilities should be considered: familial benign hypocalciuric hypercalcemia and thiazide diuretic use. Familial benign hypocalciuric hypercalcemia results from a mutation in calcium-sensing receptors that results in hypofunctioning calcium receptors in the parathyroid gland. The diagnosis is confirmed by finding an elevated serum calcium concentration in either parent or by gene analysis. A urinary calcium/creatinine ratio greater than 0.21 is considered abnormal in children 2 years of age or older. In younger children, the values are different (>0.8 in infants 6 mo and younger is abnormal), and clinicians should consult an appropriate table. (1)

If the serum phosphorus concentration is low, a serum PTH concentration should be obtained. An elevated value is consistent with the diagnosis of primary hyperparathyroidism. The excess PTH causes hypercalcemia by increasing 1,25-dihydroxyvitamin D synthesis, releasing calcium from bone, and decreasing urinary calcium excretion. The elevated 1,25-dihydroxyvitamin D concentration increases intestinal absorption of calcium and leads to hypophosphatemia through parathyroid-mediated renal phosphate wast-

ing. Primary hyperparathyroidism can be due to an adenoma, familial-associated hyperparathyroidism, and multiple endocrine neoplasia types I and II.

If the serum PTH value is low, a serum PTHrP should be measured. PTHrP, an endocrine and autocrine regulator of calcium, is homologous to PTH in the first 8 of 13 amino acids. It mimics PTH by binding PTH/PTHrP receptors in bone and kidney. Bone resorption is increased, as is distal tubular calcium reabsorption; proximal tubular phosphate reabsorption, however, is inhibited.

A detectable serum PTHrP concentration occurs in humeral hypercalcemia of malignancy (HHM). Although more common in adults than in children, HHM occurs when PTHrP is released by a tumor and leads to hypercalcemia and suppression of the patient's endogenous PTH. Malignancies of the breast, kidneys, ovaries, and bone all have been reported to secrete PTHrP. Low or normal serum PTH and significant serum PTHrP values suggest Jansen metaphyseal chondrodysplasia, a rare form of dwarfism caused by a PTH/PTHrP receptor gene mutation. Sarcoidosis is another condition in which PTHrP may be present.

If the serum phosphorus concentration is high in conjunction with a high urine calcium/creatinine ratio, 1,25-dihydroxyvitamin D should be measured. An elevated value suggests granulomatous disease, lymphoma, hypervitaminosis A or D, pheochromocytoma, adrenal insufficiency, thyrotoxicosis, thiazide diuretic or calcium carbonate use, or prolonged immobilization.

Treatment

Treatment of hypercalcemia involves not only lowering the serum calcium concentration but also treating any underlying disorder. Several methods can correct hypercalcemia. Most patients who have hypercalcemia are dehydrated at the time of presentation. Aggressive rehydration with intravenous administration of isotonic saline begins the correction by increasing urinary calcium excretion. Once the patient is rehydrated, the addition of a loop diuretic inhibits calcium reabsorption in the loop of Henle.

Long-term correction may be achieved with agents that decrease bone resorption, such as calcitonin, a bisphosphonate, or gallium nitrate. If the hypercalcemia is due to hypervitaminosis D, corticosteroids often are useful in decreasing intestinal calcium absorption. Chelation of ionized calcium using EDTA or dialysis can lower calcium concentrations quickly and dramatically, especially in patients who have cardiac disturbances or impaired renal function.

Lessons for the Clinician

Hypercalcemia presents nonspecifically and occurs with a variety of clinical disorders. The clinician must use a systematic approach to determine the cause. As more children survive primary malignancies, a growing subgroup of the pediatric population is predisposed to developing secondary malignancies. The primary pediatrician should have heightened suspicion in such patients and recognize that hypercalcemia may be the initial clue to an indolent cancer. *(Mary L. Lewis, MD, Karthik Krishnan, MD, Medical College of Georgia, Augusta, Ga.) Special thanks to Drs Roger Vega and Andrew Muir.*

Reference

1. Milliner DS. Urolithiasis. In: Avner ED, Harmon WE, Niaudet P, eds. *Pediatric Nephrology.* 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2004:1103

Case 3 Discussion

Bronchoscopy, performed to rule out the presence of a radiolucent foreign body and to observe the pulmonary architecture, revealed the presence of multiple papillomas. Recurrent respiratory papillomatosis (RRP) was diagnosed. RRP is a condition characterized by irritating or obstructing warts in the larynx, trachea, or bronchi and is caused by human papillomavirus (HPV). RRP lesions are the most common benign laryngeal tumors in children. The onset of manifestations usually is between the ages of 2 and 5 years. This child's mother denied having a history of or symptoms of HPV infection.

Differential Diagnosis

The initial determination is to delineate whether the patient has acute or chronic respiratory distress. For patients who have chronic respiratory distress with stridor, the differential diagnosis includes laryngomalacia, vascular ring or sling, tracheal hemangioma or cyst, vocal cord paralysis, and papillomatosis.

Conditions that cause stridor often are misdiagnosed as asthma and are treated with albuterol. Differentiation of stridor from wheezing, which is the hallmark of asthma (and rarely is biphasic), is an important diagnostic task.

The Condition

The most common presenting signs of RRP include hoarseness and a low-pitched voice. Due to the rarity of RRP, most patients are misdiagnosed as having more common forms of respiratory distress. Misdiagnosis is perpetuated by patients showing signs of improvement after treatment with bronchodilators, steroids, and oxygen. However, as the papillomas increase in size, bronchodilators and steroids prove to be less beneficial.

The severity of the respiratory distress is determined by the degree of obstruction.

The best method of diagnosing RRP is by seeing papillomas directly in the larynx, trachea, or bronchi, which may be achieved by use of flexible laryngoscopy or rigid bronchoscopy.

Therapy

Treatment consists of debulking the lesions, managing the airway, and reducing the recurrence of the papillomas. No standardized removal protocol exists. Most children require multiple debulking procedures throughout their lifetimes. The timing of the debulking generally is determined by the recurrence of respiratory symptoms. Rapidly progressing RRP may require debulking every other week. Complications from debulking include scarring and other iatrogenic damage to the airway. Tracheotomy should be reserved as a last resort for those patients who require constant debulking or have severely compromised airways.

Efforts aimed at reducing the recurrence of the lesions of RRP include the use of interferon, retinoids, carbinol, acyclovir, vitamin A, and antiviral agents. These medications are injected at the base of the excised lesions. The most promising hope for preventing RRP may be the newly approved HPV vaccine.

Prevention

Most physicians believe that RRP is transmitted from mothers infected with active or inactive condylomas. It is believed that when the infant passes through the birth canal, the oropharynx becomes colonized with HPV. HPV types 6 and 11 have been associated with benign RRP and types 16 and 18 with the rare forms of RRP that may convert to a malignant form.

Because HPV infection is not a reportable sexually transmitted disease, the true number of cases is not known. The Advisory Committee on Immunization Practices recommends vaccination of nonpregnant females between the ages of 9 and 26 years with HPV vaccine, which is administered in a series of three injections over a 6-month period.

Initial studies have suggested that the vaccine has an efficacy close to 100% for the prevention of diseases caused by HPV types 6, 11, 16, and 18. The vaccine may be of less benefit to females who previously have been infected with HPV. From these data, it may be extrapolated that the reduction of HPV will result in the reduction of the prevalence of RRP caused by HPV 6, 11, 16, and 18. (*Warees T. Muhammad, MD, PhD, Children's Hospital at the Medical Center of Central Georgia, Macon, Ga.; James Logan, MD, Mercer University School of Medicine, Macon, Ga.*)

Two videos showing endoscopy of patients who have respiratory papillomatosis can be viewed in the online edition of *Pediatrics in Review* (www.pedsinreview.org).

Support groups for and information regarding RRP can be accessed at www.RRPf.org, *www.RRPwebsite.org,* and www.cdc.gov/std/HPV/STDFact-HPV-vaccine.htm.

To view Suggested Reading lists for these cases, visit pedsinreview.org and click on Index of Suspicion.

Index of Suspicion

Russell Hopp, Nagendra Natarajan, Mary L. Lewis, Karthik Krishnan and Warees T. Muhammad

Pediatr. Rev. 2007;28;389-394
DOI: 10.1542/pir.28-10-389

PediatricsinReview®

Firearms

Susan Guralnick and Janet R. Serwint

Pediatr. Rev. 2007;28;396-397
DOI: 10.1542/pir.28-10-396

In Brief

Firearms

Susan Guralnick, MD
Stony Brook University Medical Center
Stony Brook, NY

Author Disclosure

Drs Guralnick and Serwint did not disclose any financial relationships relevant to this In Brief.

Gun Storage Practices and Risk of Youth Suicide and Unintentional Firearm Injuries. Grossman DC, Mueller BA, Riedy C, et al. *JAMA.* 2005;293:707–714

Firearm-related Injuries Affecting the Pediatric Population. Committee on Injury and Poison Prevention. *Pediatrics.* 2000;105:888–895

Factsheet: Firearm Injury and Death in the United States. Johns Hopkins University Center for Gun Policy and Research (rev 1/04). Available at: http://www.jhsph.edu/gunpolicy/US_factsheet_2004.pdf

Web-based Injury Statistics Query and Reporting System (WISQARS). National Center for Injury Control and Prevention, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/ncipc/wisqars/default.htm

Are Medical Societies Developing a Standard for Gun Injury Prevention? Longjohn MM, Christoffel KK. *Injury Prevention.* 2004;10:169–173

Firearm-related injury and death is a significant cause of morbidity and mortality in children and youth in the United States (US). In 2004, the Centers for Disease Control and Prevention recorded 2,852 firearm-related deaths in children and an additional 13,846 nonfatal gun-related injuries. The incidence of death resulting from gun injury is significantly higher in males than in females and as much as eight times higher in 15- to 19-year-olds than other age groups. Homicide is the second leading cause of death in adolescents and is the leading cause in African-American males ages 15 to 24, with 88% of those deaths involving guns. The US continues to have the highest rates of gun violence among developed nations. The US mortality rate from firearm injury for children 14 years of age and younger approaches 12 times the collective rate of 25 other industrialized nations.

In 2001, 35% of adults reported living in homes that contained at least one firearm. Household gun use causes the death of someone known to the family 43 times more often than the user kills in self-defense. The risk of homicide is tripled and the incidence of suicide increases five times if there is a firearm in the home. Evidence clearly demonstrates that access to guns is a significant risk factor for injury to children and adolescents. Parent-owned guns were employed in 57% of suicides and suicide attempts and in 19% of all unintended injuries and deaths by adolescents younger than 20 years. Guns present in the home of the victim, a family member, or a friend were involved in 90% of suicide attempts and 19% of unintentional injuries.

Recognizing morbidity from firearms as a serious public health issue, at least 14 national medical societies have developed policies supporting gun injury prevention. Because most children who die from a firearm injury do so before they arrive at the hospital, the 2000 American Academy of Pediatrics (AAP) statement on firearm-related injuries emphasizes prevention by encouraging absence of guns from homes and communities. Education of children, although intuitively sound, is not the answer. Several studies have demonstrated that educational interventions usually are ineffective for children and adolescents when tested in actual situations.

Data demonstrate that the most effective measures for reducing unintentional and self-inflicted firearm injuries for those who have guns in the home involve practices of safe storage. The AAP and many gun safety organizations advocate the storing of unloaded guns in a locked place, with ammunition stored and locked in a separate location. Gun-locking methods include gun lock boxes, trigger locks, and personalized safety mechanisms. High trigger pressures are recommended to make it difficult for young children to fire the weapon. In 2005, a case-control study of unintentional and self-inflicted firearm injuries to children and adolescents was published in the *Journal of the American Medical Association.* The study demonstrated that each of the previously noted safe storage practices was associated with a reduction in the relative risk of firearm injury for both unintentional and suicide injuries. Protective associations remained consistent after controlling for county of residence, age, demographics, type of firearm, number of guns in the home, and whether the gun was used for recreation or protection.

Physicians need to counsel patients and parents orally about gun safety and provide them with written information. Many resources are available for professionals and families, including Web sites and informational pamphlets provided by national and local organiza-

tions. Physicians can have a significant impact on gun safety behaviors, but to do so, they must be informed themselves.

Comment: Prevention of firearm injuries remains an important area of anticipatory guidance by the pediatrician. Morbidity and mortality arise from unintentional use, and homicides and suicides may occur on impulse and have irreversible effects. Because many gun injuries are fatal, primary prevention is essential. The data are clear about the risks of harm to children and families when a gun is in the home. Families must be informed of these risks. Although removal of guns is the most effective means of preventing morbidity and mortality, safe storage practices are the second-best means of prevention. Continued advocacy at the levels of the family, community, and state and federal legislatures is necessary.

Janet R. Serwint, MD
Consulting Editor

In Brief

Pharmacokinetics

John M. Olsson, MD
Brody School of Medicine
East Carolina University
Greenville, NC

Author Disclosure

Dr Olsson did not disclose any financial relationships relevant to this In Brief.

Pharmacologic Considerations in Antimicrobial Therapy, With Emphasis on Pharmacokinetics and Pharmacodynamics: Reviews for the Practicing Clinician. McKinnon PS, Yu VL. *Eur J Clin Microbiol Infect Dis.* 2004; 23:231–232

Antibacterial Agents in Pediatrics. Bowlware KL, Stull T. *Infect Dis Clin North Am.* 2004;18:513–531

The Therapeutic Monitoring of Antimicrobial Agents. Begg EJ, Barclay ML, Kirkpatrick CJM. *Br J Clin Pharmacol.* 1999;47:23–30

Once- Versus Twice-daily Gentamicin Dosing in Neonates ≥ 34 Weeks' Gestation: Cost-effectiveness Analyses. Thureen PJ, Reiter PD, Gresores A, Stolpman NM, Kawato K, Hall DM. *Pediatrics.* 1999;103:594–598

Pharmacokinetics describes, in mathematical terms, what the body does to an administered drug: its absorption, distribution, metabolism, and elimination. A very important linked process, pharmacodynamics, describes what an administered drug does to microorganisms and to the body: its effects and toxicity. Awareness of these principles is essential in optimizing the efficacy of drug therapy while minimizing drug-related toxicity.

When considering antimicrobial agents, it is important to recognize several factors in pediatric patients that influence pharmacokinetic and pharmacodynamic relationships. These factors include intersubject variability in plasma concentration from the same dose, the patient's age, the effects of underlying diseases, the drug-drug interactions, and how a drug is distributed in body tissues. In addition, antimicrobial agents differ in their pattern of bactericidal activity.

Given these factors, certain agents warrant monitoring of serum concentrations. Antimicrobial agents that have a wide therapeutic index and a limited risk of toxicity, such as beta-lactam antibiotics, do not require therapeutic drug monitoring. In contrast, the aminoglycosides and vancomycin have narrow therapeutic indices, and their toxicity may be significant and irreversible. Accordingly, these antimicrobial agents merit monitoring of drug concentrations.

Aminoglycosides are the mainstay of treatment of serious community-acquired and most nosocomial gram-negative bacterial infections. These drugs are used in the treatment of sepsis, meningitis, and other serious bacterial infections in neonates and also are good choices for treating community-acquired urinary tract infections in older children. Toxicity associated with aminoglycoside use includes ototoxicity, manifested by irreversible high-frequency hearing loss; vestibular toxicity; and nephrotoxicity, a reversible form of nonoliguric renal failure.

Aminoglycosides have little protein binding, and their volume of distribution is greater in infants and children than in adults, essentially representing that of the extracellular fluid space. Aminoglycosides are eliminated by the kidneys, and dosing depends on renal function, with infants typically having half the renal clearance of healthy adults. Aminoglycoside pharmacokinetics vary markedly with the state of the disease being treated. The volume of distribution and clearance change during therapy, depending on patient hydration and permeability of biologic

Firearms

Susan Guralnick and Janet R. Serwint

Pediatr. Rev. 2007;28;396-397
DOI: 10.1542/pir.28-10-396

Pharmacokinetics

John M. Olsson

Pediatr. Rev. 2007;28;397-398
DOI: 10.1542/pir.28-10-397

tions. Physicians can have a significant impact on gun safety behaviors, but to do so, they must be informed themselves.

Comment: Prevention of firearm injuries remains an important area of anticipatory guidance by the pediatrician. Morbidity and mortality arise from unintentional use, and homicides and suicides may occur on impulse and have irreversible effects. Because many gun injuries are fatal, primary prevention is essential. The data are clear about the risks of harm to children and families when a gun is in the home. Families must be informed of these risks. Although removal of guns is the most effective means of preventing morbidity and mortality, safe storage practices are the second-best means of prevention. Continued advocacy at the levels of the family, community, and state and federal legislatures is necessary.

Janet R. Serwint, MD
Consulting Editor

In Brief

Pharmacokinetics

John M. Olsson, MD
Brody School of Medicine
East Carolina University
Greenville, NC

Author Disclosure

Dr Olsson did not disclose any financial relationships relevant to this In Brief.

Pharmacologic Considerations in Antimicrobial Therapy, With Emphasis on Pharmacokinetics and Pharmacodynamics: Reviews for the Practicing Clinician. McKinnon PS, Yu VL. *Eur J Clin Microbiol Infect Dis.* 2004; 23:231–232

Antibacterial Agents in Pediatrics. Bowlware KL, Stull T. *Infect Dis Clin North Am.* 2004;18:513–531

The Therapeutic Monitoring of Antimicrobial Agents. Begg EJ, Barclay ML, Kirkpatrick CJM. *Br J Clin Pharmacol.* 1999;47:23–30

Once- Versus Twice-daily Gentamicin Dosing in Neonates ≥ 34 Weeks' Gestation: Cost-effectiveness Analyses. Thureen PJ, Reiter PD, Gresores A, Stolpman NM, Kawato K, Hall DM. *Pediatrics.* 1999;103:594–598

Pharmacokinetics describes, in mathematical terms, what the body does to an administered drug: its absorption, distribution, metabolism, and elimination. A very important linked process, pharmacodynamics, describes what an administered drug does to microorganisms and to the body: its effects and toxicity. Awareness of these principles is essential in optimizing the efficacy of drug therapy while minimizing drug-related toxicity.

When considering antimicrobial agents, it is important to recognize several factors in pediatric patients that influence pharmacokinetic and pharmacodynamic relationships. These factors include intersubject variability in plasma concentration from the same dose, the patient's age, the effects of underlying diseases, the drug-drug interactions, and how a drug is distributed in body tissues. In addition, antimicrobial agents differ in their pattern of bactericidal activity.

Given these factors, certain agents warrant monitoring of serum concentrations. Antimicrobial agents that have a wide therapeutic index and a limited risk of toxicity, such as beta-lactam antibiotics, do not require therapeutic drug monitoring. In contrast, the aminoglycosides and vancomycin have narrow therapeutic indices, and their toxicity may be significant and irreversible. Accordingly, these antimicrobial agents merit monitoring of drug concentrations.

Aminoglycosides are the mainstay of treatment of serious community-acquired and most nosocomial gram-negative bacterial infections. These drugs are used in the treatment of sepsis, meningitis, and other serious bacterial infections in neonates and also are good choices for treating community-acquired urinary tract infections in older children. Toxicity associated with aminoglycoside use includes ototoxicity, manifested by irreversible high-frequency hearing loss; vestibular toxicity; and nephrotoxicity, a reversible form of nonoliguric renal failure.

Aminoglycosides have little protein binding, and their volume of distribution is greater in infants and children than in adults, essentially representing that of the extracellular fluid space. Aminoglycosides are eliminated by the kidneys, and dosing depends on renal function, with infants typically having half the renal clearance of healthy adults. Aminoglycoside pharmacokinetics vary markedly with the state of the disease being treated. The volume of distribution and clearance change during therapy, depending on patient hydration and permeability of biologic

barriers. Patients who have severe infections, burns, or cystic fibrosis can have increased volumes of distribution, potentially necessitating higher drug doses to achieve desired peak concentrations. Higher peak concentrations also may be desirable for treating sites of infection that have less-than-optimal tissue penetration (eg, lungs, bone, central nervous system) and for serious infections.

When monitoring aminoglycosides, it is important to understand that bactericidal activity by aminoglycosides, unlike that of many other antimicrobials, depends on a high peak serum concentration rather than on the duration of a therapeutic concentration. The trough concentration is measured to identify drug accumulation that would suggest an increased risk of toxicity. A peak concentration of an aminoglycoside should be measured 30 minutes after completion of intravenous administration and a trough value within 30 minutes prior to a subsequent dose. The therapeutic ranges for peak concentrations are 6 to 10 mg/L for gentamicin and tobramycin and 20 to 30 mg/L for amikacin; aminoglycoside concentrations in excess of that range can be reduced by decreasing the dose. The trough values should be less than 2 mg/L for gentamicin and tobramycin and 5 to 10 mg/L for amikacin; increasing the dosing interval is the appropriate response to an elevated trough value. Once-daily dosing, now used widely in adult medicine, is controversial in pediatrics and has been shown to be effective only in treating newborns. Measuring trough values with once-daily dosing may be unnecessary, given the 24-hour dosage interval. Measuring concentrations of aminoglycosides after intramuscular administration is not optimal because absorption from muscle is slower and more variable, resulting in lower and less reliable values.

It is useful to compare the pharmacokinetics and pharmacodynamics of vancomycin, a glycopeptide that is active primarily against gram-positive bacteria, with those of the aminoglycosides. Vancomycin also has a narrow therapeutic index and, similar to the aminoglycosides, causes ototoxicity and nephrotoxicity. It is likely, although unproven, that toxicity is related to total vancomycin exposure. Vancomycin has moderate protein binding (55%) and is eliminated by the kidneys unchanged, with a clearance approximating that of the glomerular filtration rate. The bactericidal action of vancomycin differs substantially from that of the aminoglycosides. Vancomycin, like beta-lactam antibiotics, causes bacterial killing if the concentration of the antibiotic remains above the minimum inhibitory concentration (MIC) at all times during therapy. Therefore, it is unnecessary to measure peak concentrations as long as the trough concentration is above the MIC of the infecting organism**.** The trough range of 5 to 15 mg/L is supported by much of the literature. Adjustments in the dose in response to the trough concentration should help with clinical efficacy.

In summary, attention to the pharmacokinetics and pharmacodynamics of medications used to treat serious infections is crucial in efforts to maximize patient safety and provide optimal outcomes.

Pharmacokinetics

John M. Olsson

Pediatr. Rev. 2007;28;397-398
DOI: 10.1542/pir.28-10-397

PediatricsinReview®

The Electronic Medical Record

Mark Simonian

Pediatr. Rev. 2007;28;e69-e76
DOI: 10.1542/pir.28-10-e69

The Electronic Medical Record

Mark Simonian, MD*

Author Disclosure
Dr Simonian did not disclose any financial relationships relevant to this article.

Introduction

In 1991, the Institute of Medicine's "Report on the Computer-based Patient Record" addressed the value of the electronic record. Many basic elements were highlighted and included legible and sortable patient information, access to support for clinical decisions, entry of orders and data, enhanced communication from consultants, clinical studies about the epidemiology of medical injuries, and access to administrative data. All of these elements are expected to improve workflow, reduce errors, and provide cost savings. (1)

President Bush has said in addresses to Congress that all patients will have electronic health records by 2014. (2) His administration, with bipartisan support, has established a National Health Information Technology Coordinator Office to advise the Secretary of Health and Human Services. (3) That group helps promote development and establishes standards to make health records digital and interoperable and assures that the privacy and security of the records are protected. (4)

The American Academy of Pediatrics (AAP) first addressed the uniqueness of a pediatric electronic medical record when it published a policy statement in 2001. (5) In 2007, the policy statement was updated as a clinical report, describing additional pediatric-focused details. (6) This report is much more useful in assisting electronic medical record (EMR) vendors and organizations that establish standards to design systems that have elements critical to pediatrics and brings better value to a pediatric practice. Many elements are functionally important in pediatrics, such as immunization management, growth tracking, medication dosing, and patient identification. *Pediatric norms* need to address data elements such as numeric and non-numeric information, complex normative relationships, gestational age, adoption, guardianship, and emergency treatment.

Privacy status and sensitive information have unique ramifications in pediatrics and include elements relating to adolescent privacy, children of foster or custodial care, and consent for proxy. *Pediatric terminology* is of paramount importance when relating clinical concepts unique to pediatrics rather than employing commonly used, generalized terms in coding visits for insurance claims. *Data precision* also is necessary and should be relevant to the age of the patient. Other areas of pediatric *documentation* do not necessarily fit into the previous groupings but are necessary to complete the patient's clinical description. When advocating for future development of these elements of the EMR, standards should improve the ability of one system to exchange data with another. (6)

The AAP has been a strong proponent of the inclusion of pediatric standards by professional and governmental organizations. The Council on Clinical Information Technology and the Executive Board of the AAP support using EMRs in any pediatric practice.

Adoption of the EMR

The consideration of adopting an EMR into a pediatric practice requires thorough review. That process has been contemplated and completed by thousands of practices, although only a small percentage of all practicing pediatricians use EMRs. The highest percentage appears to be in larger group practices (about 30%), with the small group and solo practitioners falling farther behind (approximately 5% to 15% of all practitioners using these systems). (7) Because relatively few practitioners are available to consult and share their experiences in some areas of the country, this article presents a practical approach to the selection and implementation of an EMR or electronic health record (EHR). The abbreviations EMR and EHR are used synonymously throughout this article. In addition,

*Chair, Council on Clinical Information Technology, American Academy of Pediatrics.

features that pediatric users consider important in the documentation and care of patients are described.

Obstacles and Concerns

EMRs have not had high acceptance to this date for the following reasons:

- They are linked to increased computer use, which causes anxiety about implementation. Office staff members often are computerphobic, and an expectation of the need to use these technologies worries many.
- Use of complex systems necessitates the inevitable time needed for training, which detracts from time involved in practice management. Less time spent with patients because of more time devoted to the use of computers and software worries clinicians about depersonalizing patient care, as does the concept of the clinician concentrating on creating a good record and, therefore, not connecting personally with the patient.
- Costs are increasing for practices at a time when many physicians see decreasing financial return on their time, which invokes alarm.
- Practitioners fear downtime and loss of data if there is an electrical failure or loss of connection to remote systems. What will practices do if their access to information is impeded because their systems are not working?
- Change for the sake of change is not acceptable to staff or physicians. It is human nature to object if people must shift to new ways of operations when they are comfortable with their current processes.

All of these concerns are legitimate, but each can be dealt with and minimized if practices proceed carefully and have appropriate support.

Achieving Acceptance

Understanding that there are reasonable obstacles and concerns, it has been proven that EMR systems address issues of legibility, error reduction, access, and organization very efficiently. Time savings, manpower reductions, and financial returns on investment may be expected, but these benefits are harder to demonstrate in some practices. In some situations, an increase in errors has been reported with use of the EMR. In other cases, the workload has increased. Tailoring the system to the needs of the practice and providing appropriate training for all involved can maximize the benefits and minimize the adverse effects of adopting the EMR.

If staff perceives that the functions most important to the practice are provided by the new system, acceptance and adoption of the EMR system follows. If value is accepted by the decision-makers, they can campaign to educate the office staff about the changes in office operations. The adopters must have a clear idea of what changes are planned and what improvements are sought. Knowing what is needed also affects which vendor's product is chosen.

To increase the likelihood of a successful adoption, it is critical to have some physicians and staff involved in the entire process. Almost everyone in an office will be using the tools for some part of patient care. In any practice, the most influential physicians, office managers, and supervising nurses should be included. These individuals most likely will spend more time and effort in the process. Their acceptance can support the transition and selection of the specific tools and can win the cooperation of more reluctant users. Once the office is updated, all should expect dramatic changes in workflow, which require the physician to be more active in accessing and processing each encounter. The coding of the visit, retrieval of additional information, and even acquisition of relevant educational material often is accomplished by physicians. Supporting staff such as medical assistants and nurses should be included in the process.

Some practices may have reluctant adopters, and every effort must be made to have these individuals comply. Concurrent support of two systems (paper and electronic) is costly in time and efficiencies.

Analysis of Business and Technology Needs

Physicians should look closely at the strengths and weaknesses of their practices. For smaller practices, the senior physician along with the administrative supervisor may assume the responsibility of analyzing the office. By reviewing their work flow and capabilities, they can rank features they might seek in an EHR, such as electronic prescription writing or communicating with a vaccine registry. Review of the functioning of the practice is time-consuming but essential to achieve the best fit of electronic programs. One option is to hire a consultant to evaluate the practice and make suggestions. This step adds upfront costs but might help eliminate costly future errors in the selection of software and hardware. It is important to note that using a consultant does not guarantee positive results.

Processing demographic information, billing and payments, and insurer data such as addresses and rates; reporting information; analyzing practice features; and scheduling are typical elements of an electronic practice management system (PMS). Many EMR systems incorporate these tools, but some do not contain a PMS

component. Integration of the EMR and the PMS systems reduces the critical issues of interface and compatibility, especially as either system is updated. A practice already using a PMS must consider whether it will abandon the current program to adopt an integrated PMS and EMR package. The conversion does not have to be complicated, but moving patient data between original and new systems can be time-consuming and costly, and financial or demographic data might be lost. Vendors offer this service for a fee.

Practices that do not want to discontinue a current PMS must know which EMR systems can interface successfully with their existing program. Some vendors support this philosophy; others discourage the effort or will not attempt it. If a new PMS is obtained, adding new and established patients into the new system can begin with registering established patients again as they return for a visit or starting with patients new to the practice. Once the registration process has been mastered by front office staff, all patients can be entered into the new PMS.

EMR software is composed of many pieces. When discussing features of the electronic system with a potential vendor, it helps to develop questions based on individual office practices. Examining the job description of each individual can illustrate how an electronic system fits with each person's duties. This list of personnel functions is critical to the evaluation of practice management needs as well as determination of the required clinical features. Ranking the elements most important to the practice can help determine what must be included and what is optional in the final product.

Following are some features of electronic systems to consider: (8)(9)

- **Clinical Decision Support (CDS):** This term refers to electronic references that supply the practitioner with additional information that is helpful in making clinical decisions. An example of CDS is a tool that provides information about medications (indications, doses, adverse reactions, cost, and adverse effects). Vaccine registries are one of the most commonly used CDS applications, and selecting an office registry that is capable of interfacing with state registries is an important consideration.
- **Coding Assistance:** Coding assistance uses information supplied in the documentation of the encounter to determine a potential CPT code for that service. Coding assistance is a suggestion based on certain algorithms. The incorporation of new CPT or ICD-9 codes should be part of the regular updates provided by the vendor.
- **E-mail:** Most systems allow some type of messaging among users in the system. Alerts can notify receivers of messages as soon as messages are sent by using flags accompanied by bright icons or sound alerts. This methodology improves smooth communications and minimizes lost observations critical to patient safety and care. Although intraoffice communication has been a traditional piece of many EMR systems, newer requirements to share information outside the EMR have become more commonplace, including contact with other practitioners, patients, and third party payers through e-mail. Ideally, making e-mail communication part of the system allows the merging of responses into particular patient records. Patient portals (described later) point out newer features, providing methods for sharing information, including e-mail. A secure system has appropriate encryption to satisfy the Health Information Portability and Accountability Act (HIPAA).
- **Follow-up:** Practitioners can facilitate care by placing reminders in the system to follow up on encounters or set future appointments. This capability likely can improve the continuity of care.
- **Interface With Laboratories and Entry of Orders:** Electronic record systems can incorporate lists of orders that doctors use regularly and program in responses, such as requesting a complete blood count, urinalysis, and lead value at certain visits or triggering a response to certain laboratory codes, which are called LOINC codes. (LOINC® means Logical Observation Identifiers, Names, and Codes and is a public use set of codes and names for the electronic reporting of clinical laboratory test results.) A LOINC code can help to identify the order requested by the practitioner or received from a laboratory or other medical facility. The availability of lists of common orders can facilitate order writing and electronic distribution of data. When such lists are included in groups or order sets, reproducing common groups of orders reduces error by facilitating readability and ensuring that no order is forgotten. In most cases, users of the EHR can create or modify their sets of orders.
- **Patient Demographics:** Moving data between PMS and EMR systems seamlessly is very important, and reducing redundant entry by staff or physician can decrease staff time significantly. The capability to recognize multiple family names, including first and last names, is important.
- **Patient Education:** Supplementary information that can be given to the patient and family enhances and reinforces the messages that practitioners provide. Ma-

terial suitable for patients is accessible by computer from multiple sources and can be customized to the specific situation.

- **Practice Analysis:** The ability to create an easy-to-read summary of any function of a practice allows analysis and clarification of both business and clinical operations. A user should be able to customize such reports based on time, diagnosis, and patient demographics. Operational staff can identify business functions such as claims data, and clinical staff can evaluate medical trends, such as the frequency of a specific diagnosis.
- **Prescription Writing:** Prescriptions can be transmitted immediately to the pharmacy electronically or by fax. Some systems include formulary information on dosage, interactions, and costs. In pediatric systems, the ability to calculate the correct dosage of medication automatically by weight or surface area is invaluable.
- **Privacy and Security:** All patients are entitled to privacy of medical information. Adolescents are more likely to be compliant when they know that sensitive information about them is protected. Privacy tools can be built into the EHR and should be easy to implement. The ability to include or exclude sensitive portions of the chart and ensure that certain information is available only to appropriate viewers is a valuable feature. Electronic charts can be designed to allow viewing only by individuals who must see the data because of their roles in patient care. Systems should be designed to meet current HIPAA standards.
- **Generation of Reports and Analyses:** The EHR can generate reports for schools, insurers, camps, or other entities quickly and accurately. The computer captures information and puts it into usable formats needed by various parties. This function reduces redundant production of forms and can be customized to fit the practice's needs.
- **Remote Access:** Clinical information can be made available to practitioners when they are off-site through broadband Internet access. Such capability is invaluable to the practitioner who is on call and must have access to critical patient information. The electronic data are protected, secure, and easy to access.
- **Scheduling and Patient Processing:** Electronic scheduling, which is a PMS function, allows customized formatting of appointment time, permits incorporation of the practice's "ground rules" for scheduling different types of visits, and facilitates finding convenient times for patients. This tool also allows tracking of the patient at every stage of care, from waiting room through check-out. Some systems provide visual flags, adding mechanisms to calculate the time of the encounter or color code the visit by stage of the encounter. For example, the patient's name on the schedule appears green when the child is in the waiting room, yellow when in the examination room, blue after the physician completes his or her care, and red after the billing is completed. These tools also can provide important financial information for claims processing. Quick inspection of a schedule can reveal that a visit's billing was not completed because the color flags are not the right color, prompting the staff to complete necessary operations for billing.
- **Telephone Messaging:** EMRs should be designed to incorporate any telephone messages that include clinical information or demographic data. Clinicians reviewing the chart get a more complete picture than by viewing visit information only.
- **Web Portal:** Online Internet access by patients to their personal information can be provided from a secure source by employing log-ins and passwords. This mechanism allows private access to the patient or trusted persons. Information can include diagnoses at past visits, medications, and allergies. Billing information can be made available as well. E-mail requests for forms or questions about patient care can be made through this tool. Future health supervision visits can be scheduled by the family, who can be given a view of available appointments.
- **Practice Template:** In pediatric practices, routines are established after years of experience. Templates are one method to expedite the documentation of a standard operating procedure for a particular health supervision visit, a sick visit, or a procedure. Templates are part of most EMR systems. Pediatric-friendly systems may have templates preloaded and editable to meet the user's needs. If available templates are not pediatric, they should have the capability of being customized by the practice. Systems that require customization by the vendor add expense and inconvenience.

Design and Project Planning

The hardware needed to run the EMR system can be set up in a client server (CS) or application service provider (ASP) model. The CS model uses computers in the office to house the primary software. In the ASP model, primary hardware components reside in a remote facility and are maintained by the vendor. The practice must determine the degree of control it desires before deciding on the product type. The major factors are cost of setup and maintenance and owner control. Costs usually are determined by the number of physician users in either model.

The CS model requires a setup and licensing fee, which is a one-time expense. The computer is leased or owned, housed, and serviced by the practice. In addition to the initial charges, there are annual charges for maintenance and sometimes for technical support totaling around 10% to 20% of the initial license fee. The start-up (purchase) costs are much higher in the CS than the ASP model.

The ASP model requires an annual or monthly fee. The vendor houses and maintains the application through an Internet connection. The costs are smaller annually but are ongoing and, over time, can amount to substantially more than those of the CS model.

Offices must assess their resources when deciding on a purchase that may cost from $500 to $50,000 per practitioner. Costs of software, training, hardware, and technical support vary widely. Most offices already maintain some computer hardware, but more hardware and software is required for an EMR system.

Accurate inventories of currently owned technology tools must be available when investigating new systems so that vendors can address compatibility. Complete replacement versus use of present equipment and support services must be compared. Some vendors have local distributors who can supplement existing office resources or the practice might need to find new local consultants to assist in conversion or maintenance.

Selection and Procurement

Hundreds of EHR vendors are vying for physicians' business, but all are not proper fits for individual practices. Some vendors have few pediatric clients and no experience customizing necessary data elements. Some vendors cater only to institutions or large groups and do not sell directly to a solo or small group that has fewer than 60 physicians. That situation may change in the next few years because the federal government is encouraging hospitals to provide cheaper solutions to financially strapped practitioners through Stark law exemptions. These legal exemptions, aimed at allowing hospitals to subsidize medical practices, might encourage hospitals to share their licenses for practice management and clinical record systems. Some hospital systems are looking closely at the new incentives to partner with community physicians and enhance information sharing. Such legal changes are still very new; hospitals have not yet tried aggressively to partner with practitioners. The Stark exceptions have not been tested at the time of this writing and provide only partial coverage for software and hardware.

Even if some institutions cover part of the cost of implementation, practices still will be left with significant costs. It is in the practice's interest to discuss potential EHR support with hospitals before initiating the acquisition of an EMR system. The primary disadvantages for practitioners are concerns about data integrity and ownership. At a minimum, most partnerships should ensure HIPAA security and privacy.

All system vendors do not view the needs of pediatricians for documentation equally, which is important in choosing systems for practice management and clinical documentation. In an effort to categorize clinical features useful in pediatric medicine better, competition was encouraged based on a program developed at the Medical Records Institute's "Toward the Computerized Patient Record" and later at the AAP's National Conference & Exhibition meetings. "The Pediatric Documentation Challenge," which has been modified to keep the quality and features of good pediatric systems relevant to the latest capabilities of vendors, matches up to 10 vendors at a time and ranks their features in a timed scenario. (10) When this initiative was started in 2002, expectations to document privacy, immunizations, identification, and other criteria were not always met. By 2006, most competitors could document pediatric-focused scenarios well. These programs list their most recent rankings.

The Council on Clinical Information Technology web site (http://www.aapcocit.org) contains user experiences from many EHR systems and allows AAP members to contribute or view the information, in addition to providing summaries of e-mail conversation on various topics and listings of upcoming informational events.

Installation and Setup

Most practices need to purchase new hardware or upgrade some of their existing equipment. Some need to install computers in patient rooms for physician and nurse use, although often these machines are portable devices, such as laptops and tablets that move with the doctor and nurse from room to room. Fixed workstations usually are cabled into a set location. Concerns about damage or tampering often are cited as reasons for not putting computers into each examination site. Some offices choose wireless connections based on the need for mobility. Whether fixed or wireless, these computers network with a central server (one or more computers dedicated to run a software application) remotely or in the same office.

Hardware costs have decreased, and considerable processing power is available for less than $1,000 per computer. Server hardware and software costs easily can be

twice that amount. Other costs for security software and hardware, networking, backup and storing, printing, scanning, and Internet connections must be included.

The installation process can be complicated or easy, depending on the vendor. Many vendors insist that their technicians install and review the process; others complete the installation and setup from a remote system over the Internet. Depending on the installation available from the vendor, the charges may or may not be included in the initial cost.

Backup mechanisms must be developed and maintained and should be discussed with the vendor. The data must be backed up at least daily, and ongoing offsite storage of records is essential. Some services are available that allow regular storage of patient information to different regions of the country in case of local disasters or damage from hurricane, tornado, flood, or vandalism. When power outages cause temporary interruption to computers, a paper record is required. How that record will be reincorporated electronically must be discussed beforehand.

Training

Training is the element most critical to successful implementation. The leaders in the practice should be first learners and subsequently train others or the practice will need to arrange with the vendor to supply support training for all staff.

Each company has an established method for implementing training and support. Some require travel to a central location where the vendor's trainers are based. This method can be time-consuming and very expensive, involving travel, lodging, and food costs for a minimum of two or three people, depending on the size of the organization, including the physician champion, administrative staff person, and a nursing representative. An alternative method is to bring the trainer to the office(s), which is less expensive but still costly, including travel, lodging, food, and charges for trainer time. The time involved may be days or weeks, depending on the size of the practice, number of people needing instruction, and necessity of any follow-up trips. A third method is online training, which requires Internet broadband connection and a series of training sessions for all users. Some combination of all these methods may be necessary in large practices.

In most cases, initial users are expected to train subsequent users, which can reduce future costs dramatically. Initial training generally is basic, covering the essential features needed for functional start-up. Later, additional formal training may be carried out in person or online by the vendor's support staff to cover features deferred in the start-up. Paper or electronic manuals should be available, and "help" programs often are available through vendor web sites or distributed to the user through video, audio, or other automated education programs.

The costs of training and educating may be part of the initial cost of ownership but more likely are part of a maintenance arrangement with the vendor. Training costs can be up to 20% of the initial cost of the program license annually. For some vendors, however, these costs have decreased because of competitive pricing and new technologies. Flash animation, Windows® help files, PowerPoint®, text, Word® files, Internet links, and many more types of support are available. Support and training costs should be spelled out clearly in the contract. As with all features of vendor selection, the buyer should discuss training with current users of systems from various vendors.

An alternative to training physicians to enter data is to use a surrogate to document the encounter into the EMR—a scribe. Some traditional paper-based practices have used scribes to write information into the paper chart. The same philosophy can be implemented with an electronic system, employing a medical technician or assistant.

Piloting and Going Live

How the office implements an EMR system can affect its long-term success or failure. One approach is to move all office tasks to the new application at one time, which requires extensive training of most users at once. When some tasks are not understood or completed effectively, the functioning of the office slows or stops until the problem is corrected. All-at-once implementation can work if experts are available to fix things quickly, but this approach runs the risk of raising anxiety and disrupting patient care. To help reduce the impact of this all-at-once method, practices can reduce the number of patient visits temporarily, increasing them gradually as the system is learned. However, patient flow can be very difficult to control.

The other method is to adopt the changes gradually, concentrating on some patients or employing only some staff and running concurrent operations. This method takes more time but is more flexible when there are questions or problems and does not affect as many patients. Office equipment must be configured to access data in old charts while also using the new system. This method affects billing because data must be entered and used in both the old and new systems. Some clinicians have found this hybrid environment to be frustrating.

However the new EMR system is implemented, the

training and office staff must agree that there has been enough preparation and support. Support staff must be readily available during the process.

Maintenance and Support

Access to clinical and financial data is essential to the operation of the practice; there can be little downtime if practice workflow is to be efficient. Most practices do not have the interest, time, or knowledge to maintain their own systems. It is essential that users have immediate access to reliable technical support. Community hospitals or colleagues may be good sources of information about the reliability of available services. Most companies seek a monthly or annual contract to provide service based on practice size and complexity. Some vendors charge an hourly fee, which is likely to be more expensive than a monthly or annual contract. As an individual office gains more experience, other arrangements for coverage can be negotiated.

Before the arrangements are made, issues of access must be discussed and included in the contract. Some problems require immediate attention, or at least same-day attention. The contract may include additional provisions for service at times beyond normal business hours, including weekends and holidays, or provisions for repairs after hours. There can be additional charges for this extended service or for telephone or other service beyond a certain amount of time or number of calls.

Postimplementation Strategies and Enhancements

After implementation, enhancements might become available that extend beyond the scope of the contract, such as the provision of information to patients by a secure online route. Buyers should discuss how future enhancements will be presented and billed. Some EHR and practice management vendors offer packages of features that can be part of the original setup or added as the practice grows or as enhancements are needed. Such enhancements can be new elements or features not originally designed into the product. Implementation may require a onetime or annual fee. In other cases, the features are part of expected annual updates. Each practice should weigh the benefits of each feature to the patient and practice to determine the value and the return on investment. It is not in the vendor's interest to have hidden costs or applications appear without notice.

As EHRs become more popular and competition increases, most vendors will seek to incorporate niche products and services that add to the productivity of the practice or enhance information retrieval, such as new clinical decision features. As new features become available, consideration of training and implementation should be factored into the incorporation of these elements. Inadequate training can lengthen the encounter and interfere with the workflow or even increase charting errors.

Summary

Successful implementation of an EMR system requires time and organization. To select the right solution, physicians must analyze their needs and plans for future growth and functioning. With acceptance by the practice leaders, other personnel are much more likely to cooperate in choosing and implementing a system. Some systems are better choices for pediatric practices than others because of certain features used by pediatricians more frequently. During the process of selection, users should take advantage of demonstrations, on-site visits, and thorough discussions with vendors of scenarios typical of their practices, as well as profit from the experiences of colleagues. Electronic applications should be easily customizable to address changes in the practice's interests. Support and ongoing training must meet the access needs of the practice without hidden costs. Future development and updates should be incorporated into the contracts and training plans. Specific details regarding costs, services provided, and availability of support should be spelled out clearly before a contract is signed.

References

1. Institute of Medicine. *To Err is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 1999:16
2. Bush GW. *Executive Order #13335: Incentives for the Use of Health Information Technology and Establishing the Position of the National Health Information Technology Coordinator*. 2004. Available at: http://www.whitehouse.gov/news/releases/2004/04/20040427–4.html
3. *Office of the National Coordinator: Mission*. Available at: http://www.hhs.gov/healthit/onc/mission/. Accessed February 2007
4. *American Health Information Community: Background*. Available at: http://www.hhs.gov/healthit/community/background/. Accessed February 2007
5. American Academy of Pediatrics Task Force on Medical Informatics. Special requirements for electronic medical record systems in pediatrics. *Pediatrics*. 2001;108:513–515
6. Spooner SA and the AAP Council on Clinical Information Technology. Special requirements of electronic health record systems in pediatrics. *Pediatrics*. 2007;119:631–637
7. Kemper AR, Uren RL, Clark SJ. Adoption of electronic health records in primary care pediatric practices. *Pediatrics*. 2006;118:e20–e24. Available at: http://pediatrics.aappublications.org/cgi/content/full/118/1/e20
8. Adler KG. How to select an electronic health record system. *Fam Pract Mgmt*. 2005;12:55–64. Available at: http://www.aafp.org/fpm/20050200/55howt.html
9. Adler KG. Why it's time to purchase an electronic health record

system. *Fam Pract Mgmt*. 2004;11:43–50. Available at: http://www.aafp.org/fpm/20041100/43whyi.html
10. Schneider JH. Pediatric electronic health records face off in competition. *AAP News*. 2004;25:64–65

Suggested Reading and Resources

American Academy of Pediatrics. *EMR Review Project*. Available at: http://www.aapcocit.org/emr/. Accessed February 2007
Health Information Management Services Systems. *Electronic Health Record*. Available at: http://himss.org/ASP/topics_ehr.asp. Accessed February 2007
Institute of Medicine. Committee on Data Standards for Patient Safety. *Key Capabilities of an Electronic Health Record System: Letter Report*. Available at: http://www.nap.edu/catalog/10781.html
Medical Records Institute. *Toward an Electronic Patient Record (TEPR)*. Available at: http://www.medrecinst.com/conference/tepr/index.asp. Accessed February 2007

The Electronic Medical Record

Mark Simonian

Pediatr. Rev. 2007;28;e69-e76
DOI: 10.1542/pir.28-10-e69