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I have been practicing emergency medicine long enough to remember when the adult patient who presented after a syncopal spell was a clinical conundrum. We all knew that most patients who had syncope would do well, but some patients would not and a few would experience sudden death. We had little understanding or tools to sort these patient out, and therefore, admitted many for fear of missing the few.

Thanks to studies by research groups in Pittsburgh and San Francisco, we have a much better understanding of how to risk-stratify adult patients who present to the emergency department, separating them into low-risk groups that can be safely discharged and followed as outpatient and high-risk groups that benefit from admission for a more intense evaluation.

Apparent Life-Threatening Events (ALTE)

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The situation with ALTE reminds me of the confusion and uncertainty that surrounded the adult syncopal patient 20 years ago. We know that most infants who come to the emergency department after an ALTE will do well, but there is the potential for some to do poorly and there is a variable association with subsequent sudden death. Unfortunately, the ALTE evaluation process is not well defined and there are not clinically useful methods to risk-stratify patients.

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Until such methods are developed, the role of the emergency physician is to identify the ALTE event, stabilize the infant as needed, obtain key history, address any underlying causes (of which there are usually not), and provide a safe disposition (usually hospital admission). Much of the subsequent evaluation and diagnosis happen on the inpatient service, but information in this review is useful for the emergency physician to have in order to educate and comfort parents.

—J. Stephan Stapczynski, MD, Editor

Introduction

Infants with an apparent life-threatening event (ALTE) present for medical attention because an acute and unexpected change in behavior has alarmed the caregivers. These frightening episodes of apnea and color change in infants generate considerable concern in both professional and lay groups. Although such episodes may occur in children older than 12 months, the majority of patients will be younger than 1 year and predominantly younger than 6 months of age.[1,2] This age distribution and the fear engendered in the observer provide support to the possibility that such episodes, if undetected, may lead to the sudden and unexpected death of the infant. The hypothesis that these events might be premortem markers of the infant at very high risk of sudden infant death syndrome (SIDS) explains the large amount of attention, research, and clinical resources that have been focused on the problem of ALTEs in infants.[2]

Definition

The current definition of ALTE was established by the 1986 National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring:[3]

"An episode that is frightening to the observer and is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging. In some cases the observer fears that the infant has died. Previously used terminology such as 'aborted crib death' or 'near-miss SIDS' should be abandoned because it implies a possibly misleading close association between this type of spell and SIDS."

Given the subjective nature of caregiver observations and interpretation, the initial medical problem is to determine which descriptive variations of the reported episodes place the infant at increased risk for sudden death and future life-threatening episodes and which are a reflection of parental anxiety or of an acute nonrecurring problem. Consistent with the recommendations of the NIH Consensus Development Conference this differentiation often is made by assuming that reports of "frightening" episodes of apnea or respiratory difficulty are clinically of greater severity, and thus more apt to be of medical significance, if the parents also observe a change in skin color or muscle tone or provide vigorous stimulation, mouth to mouth resuscitation, or cardiopulmonary resuscitation (CPR).[4] Conversely, it often is concluded that the reported episode is not medically important if not associated with these latter observations or not requiring some type of vigorous resuscitative intervention. This assumption is made, although studies have demonstrated that parental reports of an acute event are a poor reflection of an infant's physiologic status.[2,4-6] There is a great need for research studies to examine critically the clinical implications of the ALTE characteristics by employing a variety of objectively measured outcomes. Until such time as there are objective means of adequate sensitivity and specificity to assist in making medical decisions (e.g., hospital admission, specialized clinical follow-up, home apnea monitoring), it may be necessary to rely primarily on an expression of parental concern that they had observed an episode sufficiently frightening to them to bring the infant to medical attention.[4,7]

Many infants with an ALTE can present to health care personnel without clinical signs or symptoms of significant illness.[7-10] The greatest difficulty for emergency physicians usually is deciding how to pursue a diagnosis when faced with infants who appear perfectly well. Most reports recommend a mandatory period of inpatient observation.[5,8,9] Therefore, in evaluating this group of patients, the ED diagnostic evaluation has a limited role beyond the information provided by the history and physical examination.[10]

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Table 1. Apparent Life-Threatening Events—Known Origin

INFECTION*
• Sepsis/meningitis
• Respiratory syncytial virus (RSV)
• Pertussis
• Other respiratory infections
• Urinary tract infection (UTI)
GASTROINTESTINAL*
• Gastroesophageal reflux
• Pharyngeal incoordination stimulating laryngeal chemoreceptors
• Malformations
SEIZURE*
BREATH-HOLDING SPELLS
OTHER NEUROLOGIC DISORDERS
• CNS tumor, subdural hemorrhage, hydrocephalus
• Apnea associated with Arnold-Chiari malformations
• Neuromuscular disorders
CARDIAC ARRHYTHMIAS
ABNORMALITIES OF RESPIRATORY DRIVE
• Immature respiratory center -Apnea of prematurity
• Respiratory center dysfunction -Central hypoventilation syndrome (Ondine's curse)
• Drug/toxin exposed infants
OBSTRUCTIVE SLEEP APNEA
METABOLIC, ENDOCRINE, HEMATOLOGIC
• Hypoglycemia
• Hypocalcemia
• Abnormal metabolism of fatty acids
• Electrolyte disorders
• Anemia
CHILD MALTREATMENT
• Shaken baby syndrome
• Intentional suffocation
• Munchausen syndrome by proxy (MSBP)

*Most common identifiable causes of ALTE

Incidence

Various estimates place the incidence of ALTEs in the general population at between 0.5% and 6% of all infants.[2] The higher ranges of reported incidence (4%-6%) come from studies in which parents were questioned as to whether their infant had ever turned blue or stopped breathing. However, this mode of ascertainment tends to overestimate incidence.[2,7,11] For a multitude of reasons, the true frequency and the prevalence of ALTEs are unknown.[11]

Relationship to Sudden Infant Death

The most common category of death in infancy is that which is sudden and unexplained, despite a thorough autopsy, examination of the scene of death, and review of the case history (SIDS). It is probable that the mechanisms that cause sudden and unexpected death in an infant are similar in part to some of the mechanisms that cause ALTE. This is supported by the fact that, although most studies report survival in infants who have had an ALTE, a small proportion of infants who suffer recurrent ALTE progress to sudden and unexpected death.[1] It also has been identified that a small proportion of infants who die of SIDS have a history of a previous ALTE or apnea: 7% in the National Institute of Child Health and Development Cooperative Epidemiological Study of SIDS in the U.S.[3] and 8.8% in an Australian series.[12]

ALTE and SIDS should not be considered different manifestations of the same disease process.[13] Compared with SIDS victims, infants with ALTE present earlier: they often are many weeks younger than SIDS patients.[13] Also, contrary to SIDS victims, 82% of the ALTE events occurred between 8 a.m. and 8 p.m., when the caretakers are awake.[11] With SIDS and infant safe sleeping practice education, the incidence of SIDS decreased and is currently 0.6 per 1000 live births in the United States.

Considered from a different, and perhaps more important, perspective, the incidence of sudden and unexpected death in ALTE infants appears to vary depending on the initial presentation. Those infants whose frightening episode occurred during sleep and were perceived to require cardiopulmonary resuscitation have a 10-13% risk of subsequent sudden unexpected death, even with the prescription of home monitoring devices.[3,14] Infants who responded only to resuscitation and have a subsequent similar episode, who are sibling victims of SIDS, or who develop a seizure disorder during monitoring have a greater than 25% risk of dying.[5] The precise risk for infants who experience less severe ALTE events has not been determined, but in many cases it may be no greater than that of the general population. Identification of a specific cause of ALTE does not necessarily eliminate the risk of sudden and unexpected death.[3]

For these reasons, infants who suffer ALTE have been considered an "at risk" group (for sudden death), and their study has been of particular interest with regard to the mechanisms of SIDS. This approach helps our understanding of the pathophysiology of events in living infants that may produce sudden death and complements the approaches from pathological and epidemiological studies.

Etiology

There are multiple identifiable causes of ALTEs; after evaluation approximately 50% of these infants will have a specific diagnosis.[2,3,12,14,15] Table 1 outlines main clinical diagnostic groups. Symptoms reported by parents greatly contribute to establishing most diagnoses.[1,12] As seen in Table 1, ALTE can be a symptom of many specific disorders including gastroesophageal reflux, infection, seizures, airway abnormalities, hypoglycemia or other metabolic problems, as well as impaired regulation of breathing during sleep and feeding. These episodes can occur during sleep, wakefulness, or feeding and are in infants who generally are of greater than 37 weeks' gestational age at the time of onset.[3] Clinical management of these infants does not necessarily require exhaustive

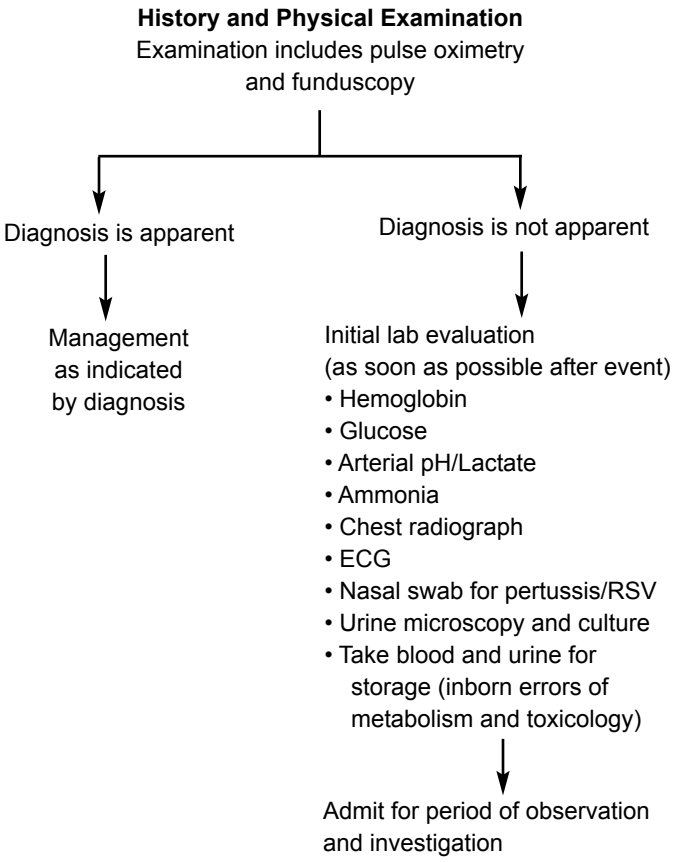
Table 2. ALTE Evaluation

CAREFUL HISTORY FROM THE PERSON WITNESSING THE EVENT

- Color (red, pale, cyanotic)
- Tone (flaccid, rigid, seizure)
- Respiratory efforts (apnea, obstructed, irregular)
- Sleep state (awake or asleep)
- Position (prone, supine, upright)
- Noises (stridor, choking)
- Eye movements (closed, startled, folled, fluttering)
- Relationship to feeding
- Fluid in mouth?
- Duration
- Need for intervention
- Environmental factors

OBTAIN PAST MEDICAL HISTORY AND FAMILY HISTORY (SEE TEXT)

Figure. Investigation of First ALTE



investigation to find an abnormality, but rather a careful and focused clinical assessment of each case, beginning with history and examination and, usually, a period of inpatient observation.

Diagnosis

Infants often appear entirely normal by the time they reach medical attention following the ALTE. Thus, the most important initial diagnostic step is to obtain a careful and detailed history. (*See Table 2.*)

A clear description of the event should be noted, including where the infant was, who was present, what each person observed, and what their actions were. The timing of the event should be noted, including whether the infant was awake or asleep and what activity he or she was performing. It may be of value to determine how it was discovered that the event was occurring. Parents or caregivers often discover such cases by chance.

A record of the infant's position should be made, whether there was movement, and how the infant was holding itself. The color of the infant should be noted—this may be red, blue, purple, pale, gray, or white. It may be possible to clarify whether color change has occurred on the face as a whole (central cyanosis), just around the eyes and mouth, or in the limbs. The presence of vomit or blood from the nose and mouth should be recorded. Vomiting may reflect infection, gastroesophageal reflux, or excessive force when doing bag, valve, mask resuscitation. Blood from the nose may be a marker for trauma and an event that is intentionally induced. The presence or absence of breathing movements should be asked about, but it may be difficult for observers to report this finding reliably. Even a nurse's observations of the presence or absence of breathing in infants receiving hospital neonatal care may correlate poorly with recorded breathing patterns.[1,16] Environmental factors also are important to elicit. Exposure to toxins such as carbon monoxide may present as an ALTE.[17]

The actions of the observers should be noted as well as the response of the infant to these actions. The time scale for these actions and the recovery of the infant should be noted and whether any similar event had occurred in the past.

A general pediatric history should be obtained of the mother's pregnancy and delivery as well as the infant's birth and neonatal progress. A history of feeding, weight gain, development, and recent minor symptoms should be noted. A detailed family medical history and social history also should be obtained. The latter should include who else is at home, other stresses and medical problems within the family, and any contact with psychiatric or social services.

The past medical history also should be probed for evidence of previous frightening episodes, abnormal breathing patterns, feeding problems, seizures, prenatal insults, and other medical problems. A family history of apnea, infant deaths, seizures, or other cardiopulmonary problems should be explored.

A full clinical examination with the infant completely undressed should be performed. The height, weight, and head circumference should be measured and plotted on a growth chart. Particular attention should be paid to examination of the upper airway and respiratory and cardiovascular systems. Neurodevelopmental assessment is important because a number of neurological conditions may present with apnea. To detect retinal hemorrhage suggestive of trauma, funduscopy should be performed. All infants should undergo initial spot measurement of arterial oxygen saturation (SpO_2); in infants who were preterm, or who may have a respiratory prodrome, a longer period of monitoring of SpO_2 should be undertaken.

After a careful history and physical examination are performed, the physician is in a position to make an initial judgment about whether the event represents an ALTE or not. If not, usually no

further diagnostic evaluation is required. If a physician believes that the infant did have an ALTE, then an aggressive approach to identifying the etiology of the event and instituting appropriate therapy is necessary. (*See Figure.*) The diagnostic evaluation may include, but is not limited to, the items listed in Table 3. Although not every infant will require all of these tests, many of them are performed before the episodes are termed "unexplained."

Management

Hospital admission for protective monitoring to facilitate the diagnostic evaluation and for parent training is recommended.[12,14,18] Parents of an infant who has suffered an ALTE may be extremely anxious and may have been concerned that their infant was dying. For this reason alone, it is probably appropriate to admit all infants who have suffered a first ALTE. This allows time for a full assessment, a period of observation, and discussion with the family.

A recurrence rate for severe ALTEs as high as 68% has been reported; episodes are more likely to recur in the few days after the first event.[1] These data provide further support for initial hospital admission. Some ALTEs may be recurrent within a short period of time (hours to days). These subsequent events may be observed and a diagnosis made by clinical observation. In addition, clinical physiological monitoring and recording allows documentation of any further events, and the findings from this may indicate a diagnosis.[1,19] Both respiratory illnesses, such as respiratory syncytial virus (RSV) and pertussis, and epileptic seizures may cluster in this way.[1]

No study has identified any single investigation as having a high positive predictive value for detecting an abnormality that will alter the outcome. There is thus much controversy as to which initial investigations should be undertaken in an infant presenting with a first ALTE. In most cases, it is not unreasonable to obtain a set of screening ancillary tests. (*See Figure, Table 3.*)

If the infant is seen very soon after the event, an arterial pH may help to provide documentation of the severity of the episode (i.e., the presence and severity of metabolic acidosis).[20] Other markers of metabolic disturbance—such as blood glucose, lactate and ammonia—also could be measured at this time. Continued observation, particularly for the development of respiratory infection, fever, or other signs of sepsis, should be undertaken, with a low threshold for treating sepsis in infants younger than 4 weeks of age. Nose swabs/pharyngeal aspirates can be collected for viral immunofluorescence and culture and for pertussis culture. Urine should be collected for microscopy, bacterial culture, and antibiotic sensitivities, and specimens also should be saved for urinary and blood metabolic and toxicologic screening.[21] Parents/caregivers may not always provide complete information about medicine given to infants, some of which may have been administered inadvertently and some deliberately.

A majority of infants suffer a single event only and survive. If the infant remains unwell, develops new symptoms, has recurrent episodes, or there is a family history of SIDS, further investigations should be undertaken. In the absence of these, investigations should be kept to a minimum in an otherwise well infant.

Infants in whom a treatable cause of ALTE can be identified are best managed by treating the specific etiology of the event (see specific disease section). Occasionally, some may require the addition of home apnea-bradycardia monitoring if ALTE can not be controlled despite specific treatment.[3,14,18,22-26]

The diagnosis of apnea of infancy (AOI) is used when an identifiable cause for the ALTE cannot be found.[3] There are presently no specific treatments for AOI, thus home apnea-bradycardia monitoring for these infants often is recommended.[3,14,18]

Table 3. Suggested Evaluation of Infants with ALTE

ALL INFANTS

- In-hospital observation with cardiorespiratory monitoring
- Careful physical and neurologic examination
- Complete blood count
- Blood glucose, electrolytes, calcium, phosphate, bicarbonate, magnesium, and ammonia
- Chest roentgenogram
- Electrocardiogram
- Urinalysis and urine culture

SELECTED INFANTS UNDER CERTAIN CLINICAL CIRCUMSTANCES

- Septic workup (blood, urine, CSF cultures)
- Barium swallow
- Laryngoscopy, bronchoscopy
- Radionuclide milk scan of swallowing
- Esophageal pH study with multichannel recording
- Ultrasound or computerized tomography scan of the brain
- Echocardiogram
- Electroencephalogram
- Polysomnogram
- Evaluation for inborn errors of metabolism
- Holter monitoring
- Urine toxicology screen
- Skeletal survey
- Covert video surveillance

Specific Causes of ALTE

Infections. Apnea can be the initial presenting symptom in some infants with respiratory syncytial virus (RSV) infections.[27-30] Although the apnea can be life-threatening, episodes usually are of short duration and occur during the first week of illness. Apnea in infants with RSV bronchiolitis occurs most commonly in young infants (younger than 3 months) with a history of premature birth and apnea of prematurity.[27,29] The apnea occurs primarily in quiet sleep and is not obstructive.

The exact pathophysiology of apnea in RSV infection remains unclear. Lindgren et al suggested that RSV might alter the sensitivity of the laryngeal chemoreceptors leading to laryngeal chemoreflex and central apnea. This reflex can be prolonged and even fatal.[31]

Infants with bronchiolitis also may develop apnea from increased work of breathing, respiratory muscle fatigue, and hypoxemia.[28]

Apnea also may complicate other infections including meningitis, encephalitis, bacterial sepsis, botulism, pertussis, and other respiratory infections.[31]

Discussions of the differential diagnosis in children presenting with an ALTE often do not mention urinary tract infection (UTI), but a causal link between UTI and ALTE has been made.[32] Therefore, if another cause of ALTE is not found, it is suggested that clinicians obtain a urine culture.

Seizure-Induced ALTE. Seizures can be associated with apnea and hypoxemia. Seizures have been shown to occur in 4-15% of infants with ALTE, and such infants have a particularly high risk of sudden death.[3,12,33] However, it often is difficult to prove whether seizures have resulted from or were caused by an ALTE. Usually, the possibility of seizure-induced events is considered on clinical grounds (e.g., clustering of attacks, facial/eye movements, or an increase in muscle tone); however, apnea may occur as the only clinical manifestation of seizures in neonates, infants, and young children.[34-36]

ALTEs that result from seizure disorders frequently follow a characteristic pattern when carefully studied. First, there is a change in the electroencephalogram (EEG), followed by one or more pauses in breathing movements, and ultimately a decrease in oxygen saturation.[34]

EEG is a recommended procedure in the investigation of ALTE. Some advocate that central nervous system disorders should be excluded in infants with an ALTE, even in the absence of clinical clues.[33]

Airway Obstruction. Investigators using overnight polysomnography have found that following an ALTE, infants have increased obstructive and mixed apneas compared to non-risk groups.[15,37-40] The obstructed breaths occur mainly in rapid eye movement sleep and are accompanied by drops in heart rate and saturation.[37] Some infants who have ALTEs later die of SIDS. These infants also are noted to have more frequent episodes of regurgitation after feeding and to move less during sleep.[37] Such findings are in agreement with reports suggesting that although obstructive apneas are rare in normal infants,[41] they may play a role in ALTE and in SIDS.[15,37-40] Obstructive apneas may be related to craniofacial malformations, gastroesophageal reflux, bulky arytenoid apparatus, central nervous system disorder, or vascular malformations.[15,42,43]

Recent evidence suggests that there is a relationship between obstructive sleep apnea (OSA) in adults and sudden unexpected infant death/ALTE in their biologic relatives.[44-46] Familial factors influencing this association may include the degree of the predilection for OSA, liability for respiratory illness or allergy, dimensions of the oral-pharyngeal airway, and ventilatory response to hypoxia.[44] These findings suggest that SIDS and ALTE are related to OSA.[45] Polysomnography is required to establish the diagnosis of obstructive apnea, as history often is misleading.[42]

Breath-Holding Spells (BHS). Cyanotic breath-holding episodes have been appreciated as a medical problem in pediatrics for many years. They are a common phenomena with approximately 3% of all children manifesting these episodes sometime during their early childhood. More than 25% begin before 6 months of age.[47]

There are two main clinical features of cyanotic breath-holding episodes: a) The first is a prolonged expiratory apnea; and b) the second is the rapid development of central cyanosis, reflecting severe hypoxemia.[48]

Episodes usually begin in response to a sudden painful or unpleasant stimulus with the infant or child becoming rapidly cyanotic (usually within 5 seconds of the onset of the event) and holding his/her breath. The characteristics of the breath-holding are that of prolonged expiratory efforts without inspiratory efforts. However, on some occasions the cyanosis may occur despite continued breathing.[49]

Although the episodes often are precipitated by a cry or an attempt to cry, during the episodes the patient usually remains silent. As the apnea and cyanosis progress, the patient may develop an opisthotonic posture, usually at around 10 to 20 seconds into the attack. Loss of consciousness usually occurs within 30 seconds and may be followed by a generalized seizure.[50] Recovery is heralded by a gasp, which often appears to be stimulated by a sudden shock to the patient, such as the application of cold water, blowing in the face, or an attempt at mouth-to-mouth resuscitation. On recovery from an episode, the patient may remain drowsy, pale, and may sleep for several hours. Sometimes one attack will follow another within minutes with the succeeding episodes being more severe. From the parental point of view, these are frightening situations and many parents believe their child to be dying during such episodes. The application of mouth-to-mouth resuscitation by parents in this situation is not uncommon. In many patients with such cyanotic/apneic episodes, crying without apnea also is accompanied by central cyanosis.

In the majority of instances, the cyanotic breath-holding episodes begin within the first year of life, with some starting within the first few days of life.[50] In one report the symptoms began at a median age of 7 weeks, and 77% began at less than 4 months.[49]

Central nervous system sympathetic activity in response to an environmental stimuli (stress) is felt to produce the prolonged expiratory apnea through effects on the brainstem respiratory centers and right-to-left intrapulmonary shunting through effects on the pulmonary vasculature. These episodes are involuntary and reflexive and occur during active or full expiration.[50]

Infants and children with BHS can manifest other signs of autonomic dysfunction.[49-52] Infants with BHS have breathing disorders during sleep. Compared to a control group, infants with BHS have obstructed breathing, snoring, and sweating during sleep.[51]

Breath-holding spells have been associated with several structural neurologic problems including medullary tumor, bilateral abductor vocal cord paralysis, hydrocephalus, and Arnold Chiari malformation. An association with complex partial seizures has been described.[53]

Pallid BHS are associated with severe bradycardia or asystole, whereas cyanotic BHS are not.[52] Pallid BHS is a misnomer, for they are not breath-holding spells at all, but rather vasovagal syncope.

The evaluation of BHS consists of a careful history. Laboratory testing usually is not indicated unless accompanied by other findings on neurologic examination. Treatment consists of parenteral reassurance. The spells are outgrown, usually without residua.

Gastrointestinal Causes of ALTE. A high percentage of identifiable etiologies of ALTE are the result of a gastrointestinal

problem.[12] Investigation of a potential gastrointestinal cause for an ALTE begins with the history, which often is the most important part of the entire GI evaluation. Specific questions pertinent to GI-related causes of the event(s) include:

Was the episode related to feedings? If there seems to be a temporal association between feeding and the events, it is important to differentiate distress during swallowing from distress after the infant finishes a meal. This may differentiate structural problems, such as H-type tracheoesophageal fistula (TEF) or laryngeal cleft, from gastroesophageal reflux (GER) induced events. In the newborn period, feeding occasionally may be accompanied by symptoms such as coughing and choking, and signs such as cyanosis and apnea. These feeding-related problems may be life-threatening.[54] An upper gastrointestinal series (UGI) should be the first radiological study in these patients; it will be diagnostic in patients with an H-type TEF or any other anatomical problem. However, in patients with a normal UGI and continued symptoms, a modified barium swallow should be performed to exclude swallowing dysfunction and aspiration.[54]

If the events occur after a feeding, how long after? Often, infants with GER have an associated delay in gastric emptying that may manifest as regurgitation of milk many hours after it was ingested.[55]

Does vomiting occur, or was there evidence of regurgitation during the event? While half of all healthy infants between 2 and 8 months of age regurgitate two or more times each day, and 15% vomit three or more times daily, regurgitation leading to an ALTE is considered a red flag for pathological GER and requires further evaluation.[56,57]

Have there ever been any problems with weight gain? Undernutrition due to excessive vomiting or poor intake due to pain with eating can lead to growth problems, and also is considered a red flag for pathological GER, requiring further evaluation. However, certain central nervous system disorders (e.g., diencephalic syndrome) or metabolic diseases may manifest with poor weight gain and ALTE.

Contrast radiography using barium generally is the best study to define the anatomy of the upper digestive tract in infants with ALTE. Anatomic abnormalities of the esophagus, cardioesophageal junction, gastric outlet, and duodenal sweep are easily defined in this manner. More unusual anatomic causes of ALTE, such as gastric volvulus can be identified with contrast radiography.[58] The test is widely available and generally not invasive or cost-prohibitive. However, because it is a static rather than dynamic test, it is neither sensitive nor specific in diagnosing GER.

Gastroesophageal Reflux. Gastroesophageal reflux (GER) is characterized by the effortless passage of gastric contents into the lower esophagus. Reflux can be classified as physiologic, in which the infant remains free of clinical sequelae, and pathologic reflux or gastroesophageal reflux disease (GERD), in which gastrointestinal, pulmonary, or neuropsychiatric complications are associated with intraesophageal acidification.[56] A classification that is particularly useful to the clinician categorizes reflux by its expected natural history. Thus, infantile reflux, which results from a delay in the acquisition of normal upper gastrointestinal motility, is likely to resolve by the first birthday. In contrast, childhood GER, although it may begin during infancy, appears to be a chronic disorder similar to reflux encountered in the adult population.

Symptoms due to reflux are summarized in Table 4.[55,59-61] Infantile apnea remains the most controversial of the possible relationships between GER and pulmonary disease. Intraesophageal acidification results in two clinically distinct patterns of apnea. Awake apnea is characterized by a sudden staring or startled appearance within the hour after a feeding and often is preceded by a change in position.[62] A history of choking, coughing, or vomiting is obtained for a minority of these infants. Spitzer and colleagues have confirmed the temporal relationship between intraesophageal acidification and awake apnea and the response of these infants to anti-reflux therapy.[35] The majority of these children had some degree of obstructive apnea during the periods of GER.

Although there is general agreement that awake apnea is reflux related, there is less consensus regarding the relationship between sleep apnea or ALTE and GER. Attempts at confirming a temporal relationship between reflux and sleep apnea have produced variable results.[56] Episodes of reflux occur more frequently in infants when awake than when asleep, although when episodes do occur during sleep they tend to be of longer duration.[65] It has been suggested that the duration and not the frequency of these episodes during sleep may be an important determinant of both reflux-associated respiratory disease and ALTE.[63-65] Nocturnal reflux is uncommon, but when it occurs in infants it is more apt to occur during active sleep than during quiet sleep. In infants, active (rapid eye movement) sleep is accompanied by reduced pulmonary oxygen reserves, depressed respiratory muscle responsiveness, and reduced upper esophageal sphincter pressure; therefore, reflux during sleep may occur at a time of increased vulnerability of the respiratory system.[66] Children with prominent nocturnal cough and wheezing are especially likely to have nocturnal reflux. Additionally, nocturnal reflux predisposes to esophagitis because of the prolonged esophageal acid exposure that occurs during sleep.[66]

Another mechanism by which GER or pharyngeal incoordination causes apnea is by stimulation of chemoreceptors around the larynx that respond to a variety of stimuli such as gastric acid and water; the reflex response is comprised of central apnea, bradycardia, and pallor due to central pooling of blood.[2] In the older infant, the more mature response includes swallowing.

In infants, a pattern of isolated bradycardia associated with irregular respiration while sleeping is highly suggestive of GER and should prompt further evaluation and treatment.[67]

Apnea may arise from either esophageal or laryngotracheal reflux events. This can occur from the presence of direct aspiration, altered gas exchange or stimulation of the laryngeal chemoreceptor reflux.[59] An acid solution instilled into the esophagus can provoke obstructive apnea, as well as central and mixed apnea, and is related to maturity.[68]

Many studies support the sequence of events in which GER provokes the apneic episode. In infants with severe GER, irregular breathing frequently is observed.[68] Furthermore, conservative or surgical treatment of GER decreases the apneic events.

In contrast to the proposed mechanism of GER leading to

Table 4. Symptoms of GERD

SYMPTOMS DUE TO REGURGITATION

- Emesis with weight loss
- Failure to thrive
- Dental enamel erosion
- Recurrent otitis media

SYMPTOMS DUE TO ESOPHAGITIS

- Chest pain, irritability, feeding problems
- Anemia
- Hematemesis
- Esophageal obstruction due to stricture

RESPIRATORY SYMPTOMS

- Croup, otitis media, sinusitis
- Pneumonia (especially recurrent or chronic)
- Wheezing, bronchospasm (especially intractable asthma)
- Apnea, cyanotic episodes (especially obstructive apnea)
- Complex respiratory disease-reflux interactions
  - -Esophageal atresia and tracheoesophageal fistula
  - -Cystic fibrosis
  - -Bronchopulmonary dysplasia
  - -Neurologic impairment
- Miscellaneous: stridor, cough, hiccups, hoarseness, nasal obstruction

NEUROBEHAVIORAL SYMPTOMS

- Infant "spells" (including seizure-like events)
- Sandifer syndrome (atypical torticollis)

apnea, other investigators have suggested a reversed order of events (i.e., apnea followed by GER).[68,69] Arad-Cohen et al examined the temporal relationship between GER and apnea in 21 infants with intermittent episodes of reflux and a history of ALTEs.[68] They concluded that GER is frequent in infants with an ALTE, and obstructive and mixed apnea preceded the GER. The increased frequency of mixed and obstructive apnea in infants with ALTEs raises the question of whether the two phenomena coexist in this patient population as a result of maturational defect in the central control of the upper airway and the lower esophageal sphincter.[69] Both structures are under the control of the central autonomic network located in the nucleus tractus solitarius in the dorsal region of the medulla ventral to the dorsal vagal nucleus.[69]

The infant presenting with an ALTE and symptoms suggestive of GER is best evaluated with a 24 hour intraesophageal pH study. This test has been the gold standard in identifying pathological GER for more than 20 years.

Inborn Errors of Metabolism. The rare association between inborn errors of fat oxidation and ALTE or with SIDS-like deaths has been described.[21,70] An inborn error of metabolism is more likely to be associated with an ALTE if the initial ALTE is severe and if there is a family history of ALTE, consanguinity, seizure disorders, or SIDS.[21] Inborn errors of fat oxidation may be apparent only during times of metabolic stress, such as fasting associated with an infectious illness when the infant is forced to utilize fatty acids rather than carbohydrates as substrates for energy production. The clinical presentation may include nonketotic-hypoglycemic attacks in a previously healthy infant, triggered by a physical stress or a period of fasting. Progression of symptoms may mimic an ALTE. Medium chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common of these disorders and the most likely to present as an ALTE. Inborn errors of beta-oxidation of fatty acids can cause up to 4% of severe ALTE and up to 5% of cases of SIDS.[21,70] Treatment of MCADD involves the avoidance of fasting, L-carnitine supplementation, a low-fat/high carbohydrate diet, and home apnea-bradycardia monitoring for infants with ALTE.

Each infant with an ALTE should have blood NH_4 measured as a screening test. A more thorough diagnostic evaluation is recommended for ALTE infants with: 1) an elevated serum NH_4; 2) a positive family history for AOI, seizure disorders, SIDS, or other sudden infant deaths; 3) laboratory evidence of hypoglycemia, hyperammonemia, metabolic acidosis, elevated liver enzymes, or abnormal hemostasis; and/or 4) a patient history of unexplained failure to thrive, developmental delay, or seizures. This includes blood and urine carnitine, urine nonvolatile organic acids, urine acylglycine, and blood and urine acylcarnitines.

Nonaccidental Head Injury. The first reports of child abuse presenting as ALTE occurred in 1979.[71] Since then, multiple publications have documented an association between child abuse and ALTEs.

The link between ALTEs and abusive head injury was confirmed in 1995 when 5 patients admitted for evaluation of an ALTE were found to have shaken baby syndrome.[72] The initial history and physical examination revealed no apparent cause, but the discovery of retinal hemorrhages in 4 of the infants and the development of focal seizures in the fifth patient prompted further evaluation that led to the diagnosis of child abuse.

In two recently reported series, 1 in 40 ALTE admissions were linked to abusive head injury.[73,74] Because an infant who has sustained an abusive head injury may appear well on presentation, with no external signs of abuse,[75,76] intentional head injury must be considered in a patient who has an ALTE unless an alternative cause is readily apparent. Therefore, unless history, physical examination, and initial test results strongly suggest another cause, the clinician should consider an evaluation for possible inflicted injury, beginning with a dilated funduscopic examination and brain imaging studies.

Several forms of child abuse other than inflicted head injury have been implicated in ALTEs: intentional poisoning, intentional smothering, and Munchausen syndrome by proxy.[77] Because all of these are difficult to diagnose, physicians must be vigilant to avoid overlooking instances of child abuse.

Munchausen Syndrome by Proxy (MSBP)/Factitious Illness by Proxy. Child abuse as a cause of ALTE is the most difficult to diagnose. The circumstances associated with child mistreatment may range from a sudden isolated loss of control by a parent to circumstances in which there is a long-standing catalog of premeditated and intentional acts of harm to the child. The latter form of abuse may involve injuries such as fractures of different ages, deliberate burns or scalds, pinch or human bite marks,

and the induction of illness in the child.[20] One particular symptom, namely recurrent apneic or cyanotic episodes, may have occurred as a result of intentional suffocation.[19,20,77-83]

Munchausen syndrome is a bizarre illness in which a patient either fabricates or actually causes symptoms that require medical intervention. First described by Asher in 1951, the name is derived from Baron von Munchausen, an 18th century mercenary who became known for fanciful and wildly embellished tales of his travels abroad.[84] Munchausen syndrome by proxy (MSBP), first described in 1977 by Meadow, is a form of child abuse in which a parent, usually the mother, systematically fabricates information about her child's health or intentionally makes the child ill.[85]

When a parent induces a life-threatening illness or fabricates an illness, resulting in invasive diagnostic, anesthetic, or surgical procedures for the child, the case becomes one of child abuse.[86] The psychodynamics involved in these situations are quite different from those operative in the typical child-abusing parent.[86] The parent who is causing the illness (most often the mother) displays model behavior and therefore the diagnosis of induced or factitious illness often is unsuspected and hence delayed. In one review, the mean time for onset of signs and symptoms of illness to the diagnosis of MSBP was 14.9 months.[87] Given the 10% mortality associated with the syndrome, early awareness of the associated signs and symptoms by physicians is important.[88]

The most common presenting signs for MSBP are bleeding (44%), seizures (42%), central nervous system depression (19%), apnea (15%), diarrhea (11%), vomiting (10%), fever (10%), and rash (9%). The most common methods of fabricating illness are lying, poisoning, suffocating, specimen tampering, and chart falsifying.[87-89]

Thorough discussion of MSBP must address the uncanny ability of the parent to fool doctors and the susceptibility of physicians to the parent's manipulations. Factors that should raise suspicion of MSBP have been suggested in numerous publications and are presented in Table 5.[80,85,87-89]

Apnea frequently has been described as a manifestation of MSBP, and conclusive proof of the parent's role has been provided by the use of covert video surveillance (CVS) to film the mother during the act of asphyxiating the child.[20,88]

Techniques used by these parents to asphyxiate their infants include covering the mouth or nose with one or both hands, a piece of cotton fabric, an article of the patient's clothing, domestic plastic film, a pillow, holding the child tightly to their chest, and also inserting the fingers into the back of the mouth.[20,77,80] Infants struggle violently, but there often are no cutaneous markings. If present, bleeding from the nose or mouth in association with an ALTE distinguishes intentional suffocation from ALTE attributable to natural causes.[20] The presence of erythema over the nose or face also should raise the possibility of intentional suffocation.

It has been suggested that the presence of bleeding from the nose, mouth, or both and a family history of sudden death in childhood should dictate a full and forensic analysis of the family history, including information from social services and other child protection agencies, the police, emergency departments, and the family physician.[20] There should be a low threshold for performing a skeletal survey, retinal examination, and brain imaging. Siblings also should be examined and their records reviewed.

Table 5. Guidelines for Suspecting Munchausen Syndrome by Proxy (MSBP)

- A child who has an unexplained, prolonged, and extraordinary illness. The medical problems do not respond to treatment.
- Physical and laboratory findings made in relation to the illness cannot be explained, are very unusual, or are considered implausible.
- A parent (usually the mother) who appears to be medically knowledgeable and/or fascinated with medical details, appears to enjoy the hospital environment, and often expresses interest in the details of other patients' medical problems. The suspected parent may work in the health care field herself or profess interest in a health-related job.
- A highly attentive parent who is reluctant to leave her child's side and who herself seems to require constant attention.
- A parent who appears to be unusually calm in the face of serious difficulties in her child's medical course while being highly supportive and encouraging of the physician, or one who is angry, devalues staff, and demands further intervention, more procedures, and the like.
- The signs and symptoms of a child's illness do not occur in the parent's absence (hospitalization and careful monitoring may be necessary to establish this causal relationship).
- A family history of similar sibling illness or unexplained sibling illness or death. The family history also may disclose numerous medical problems that are difficult to substantiate.
- A suspected parent with an emotionally distant relationship with her spouse; the spouse often fails to visit the patient and has little contact with physicians even when the child is hospitalized with serious illness.

Deliberate human actions are likely to explain a small part of SIDS and ALTE events. The American Academy of Pediatrics estimates that fewer than 5% of apparent SIDS deaths are due to abuse.[90] They occur, however, and must be considered particularly in light of the implications for subsequent mortality and morbidity in siblings and other infants harmed by a repeat perpetrator.

The term MSBP has been used both as a descriptor of the abuse itself (pediatrics) and as a diagnostic label for the perpetrator (psychiatry). The latest DSM-IV manual has replaced the term MSBP with factitious illness by proxy.[89] The diagnosis applies to perpetrators who intentionally produce or feign symptoms in another person under their care and are motivated by a need to assume the sick role by proxy.

It is essential to distinguish MSBP from other forms of child abuse that may involve illness falsification. In the last 5 years, a multidisciplinary group convened by the American Professional

Society on the Abuse of Children (APSAC) has developed specific diagnostic criteria with review and input from several professional societies.[88] The APSAC definitions created the specific term "pediatric condition falsification" (PCF) to be used for the diagnosis of the abuse in the child. Another term, factitious disorder by proxy (FDP), is used to describe the diagnosis in the caretaker who harms her child through PCF with the motivation of "self-serving psychological needs." MSBP is retained in the APSAC guidelines as a descriptor for the disorder that contains both these elements because of its acceptance and familiarity in the medical community.

Conclusion

Infants with an ALTE form a heterogeneous entity. A large array of diagnoses can be found. In approximately 50% of the cases a specific medical or surgical cause can be found for the event. A systematic diagnostic evaluation of infants with an ALTE, together with a comprehensive treatment program is necessary to increase the possibility of quality survival for these infants.

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Physician CME Questions

31. A 2-month-old boy suddenly became limp, cyanotic, and apneic. He was revived with mouth-to-mouth resuscitation. When he was seen in the emergency room, findings on physical examination were normal. Of the following, the *most* appropriate next step in the management of this patient is to:
    A. admit to the hospital for evaluation.
    B. discharge to home with an apnea monitor.
    C. reassure the parent that this is unlikely to happen again.
    D. schedule a follow-up visit in 1 week.
    E. schedule polysomnography on an ambulatory basis.

32. All of the following symptoms and findings are associated with gastroesophageal reflux, *except:*
    A. failure to thrive.
    B. anemia.
    C. recurrent pneumonia.
    D. supraventricular tachycardia.
    E. atypical torticollis.

33. All of the following are true statements regarding gastroesophageal reflux (GER) in infants and children *except*:
    A. Apnea may be a complication without obvious emesis.
    B. Nocturnal reflux may cause cough and wheezing.
    C. The "gold standard" for diagnosing pathologic GER is sampling of tracheobronchial secretions for detection of lipid-laden macrophages.
    D. Reflux episodes occur in healthy pediatric patients.

34. The NIH definition of ALTE includes all the following factors *except:*
    A. apnea.
    B. CPR is required to interrupt to event.
    C. color change.
    D. change in muscle tone.

35. The most common identifiable causes of ALTEs are infection, gastrointestinal causes, and seizure.
    A. True
    B. False

36. All of the following statements about ALTE in infants are true *except*:
    A. There are multiple identifiable causes of ALTEs, and after evaluation approximately 90% of these infants will have a specific diagnosis.
    B. Obstructive apnea may play a role in ALTEs.
    C. Gastroesophageal reflux (GER) may result in an ALTE in awake and asleep infants.
    D. The infant with an ALTE and symptoms suggestive of GER is best evaluated with a 24-hour intraesophageal pH study.

37. All of the following are known causes of ALTE in infants *except*:
    A. seizure disorder.
    B. GER.
    C. otitis media.
    D. inborn error of fat oxidation.

38. Which one of the following statements about Munchausen syndrome by proxy (MSBP) is *not true*?
    A. MSBP is a form of child abuse in which a care-taker fabricates information about their child's health or intentionally makes the child ill.
    B. The person causing the illness in the child is most often the father.
    C. Common presentations of MSBP are bleeding, seizures, apnea, and vomiting.
    D. One identifiable cause of ALTE is intentional suffocation of the infant.

39. Breath-holding spells may be associated with:
    A. autonomic dysfunction.
    B. structural neurologic problems such as brain tumor.
    C. hydrocephalus.
    D. all of the above.

40. When considering family history during an ALTE evaluation, all of the following are considerations *except*:
    A. apnea.
    B. migraine.
    C. infant death.
    D. seizure disorder.

CME Answer Key

31. A; 32. D; 33. C; 34. B; 35. A; 36. A; 37. C; 38. B; 39. D; 40. B

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Apparent Life-Threatening Events

Apparent Life-Threatening Events—Known Origin

INFECTION*
- Sepsis/meningitis
- Respiratory syncytial virus (RSV)
- Pertussis
- Other respiratory infections
- Urinary tract infection (UTI)

GASTROINTESTINAL*
- Gastroesophageal reflux
- Pharyngeal incoordination stimulating laryngeal chemoreceptors
- Malformations

SEIZURE*

BREATH-HOLDING SPELLS

OTHER NEUROLOGIC DISORDERS
- CNS tumor, subdural hemorrhage, hydrocephalus
- Apnea associated with Arnold-Chiari malformations
- Neuromuscular disorders

CARDIAC ARRHYTHMIAS

ABNORMALITIES OF RESPIRATORY DRIVE
- Immature respiratory center
  -Apnea of prematurity
- Respiratory center dysfunction
  -Central hypoventilation syndrome (Ondine's curse)
- Drug/toxin exposed infants

OBSTRUCTIVE SLEEP APNEA

METABOLIC, ENDOCRINE, HEMATOLOGIC
- Hypoglycemia
- Hypocalcemia
- Abnormal metabolism of fatty acids
- Electrolyte disorders
- Anemia

CHILD MALTREATMENT
- Shaken baby syndrome
- Intentional suffocation
- Munchausen syndrome by proxy (MSBP)

*Most common identifiable causes of ALTE

ALTE Evaluation

CAREFUL HISTORY FROM THE PERSON WITNESSING THE EVENT
- Color (red, pale, cyanotic)
- Tone (flaccid, rigid, seizure)
- Respiratory efforts (apnea, obstructed, irregular)
- Sleep state (awake or asleep)
- Position (prone, supine, upright)
- Noises (stridor, choking)
- Eye movements (closed, startled, folled, fluttering)
- Relationship to feeding
- Fluid in mouth?
- Duration
- Need for intervention
- Environmental factors

OBTAIN PAST MEDICAL HISTORY AND FAMILY HISTORY (SEE TEXT)

Suggested Evaluation of Infants with ALTE

ALL INFANTS
- In-hospital observation with cardiorespiratory monitoring
- Careful physical and neurologic examination
- Complete blood count
- Blood glucose, electrolytes, calcium, phosphate, bicarbonate, magnesium, and ammonia
- Chest roentgenogram
- Electrocardiogram
- Urinalysis and urine culture

SELECTED INFANTS UNDER CERTAIN CLINICAL CIRCUMSTANCES
- Septic workup (blood, urine, CSF cultures)
- Barium swallow
- Laryngoscopy, bronchoscopy
- Radionuclide milk scan of swallowing
- Esophageal pH study with multichannel recording
- Ultrasound or computerized tomography scan of the brain
- Echocardiogram
- Electroencephalogram
- Polysomnogram
- Evaluation for inborn errors of metabolism
- Holter monitoring
- Urine toxicology screen
- Skeletal survey
- Covert video surveillance

Investigation of First ALTE

History and Physical Examination
Examination includes pulse oximetry and funduscopy

- Diagnosis is apparent → Management as indicated by diagnosis
- Diagnosis is not apparent → Initial lab evaluation (as soon as possible after event)
  - Hemoglobin
  - Glucose
  - Arterial pH/Lactate
  - Ammonia
  - Chest radiograph
  - ECG
  - Nasal swab for pertussis/RSV
  - Urine microscopy and culture
  - Take blood and urine for storage (inborn errors of metabolism and toxicology)

→ Admit for period of observation and investigation

Symptoms of GERD

SYMPTOMS DUE TO REGURGITATION
- Emesis with weight loss
- Failure to thrive
- Dental enamel erosion
- Recurrent otitis media

SYMPTOMS DUE TO ESOPHAGITIS
- Chest pain, irritability, feeding problems
- Anemia
- Hematemesis
- Esophageal obstruction due to stricture

RESPIRATORY SYMPTOMS
- Croup, otitis media, sinusitis
- Pneumonia (especially recurrent or chronic)
- Wheezing, bronchospasm (especially intractable asthma)
- Apnea, cyanotic episodes (especially obstructive apnea)
- Complex respiratory disease-reflux interactions
  -Esophageal atresia and tracheoesophageal fistula
  -Cystic fibrosis
  -Bronchopulmonary dysplasia
  -Neurologic impairment
- Miscellaneous: stridor, cough, hiccups, hoarseness, nasal obstruction

NEUROBEHAVIORAL SYMPTOMS
- Infant "spells" (including seizure-like events)
- Sandifer syndrome (atypical torticollis)

Guidelines for Suspecting Munchausen Syndrome by Proxy (MSBP)

- A child who has an unexplained, prolonged, and extraordinary illness. The medical problems do not respond to treatment.
- Physical and laboratory findings made in relation to the illness cannot be explained, are very unusual, or are considered implausible.
- A parent (usually the mother) who appears to be medically knowledgeable and/or fascinated with medical details, appears to enjoy the hospital environment, and often expresses interest in the details of other patients' medical problems. The suspected parent may work in the health care field herself or profess interest in a health-related job.
- A highly attentive parent who is reluctant to leave her child's side and who herself seems to require constant attention.
- A parent who appears to be unusually calm in the face of serious difficulties in her child's medical course while being highly supportive and encouraging of the physician, or one who is angry, devalues staff, and demands further intervention, more procedures, and the like.
- The signs and symptoms of a child's illness do not occur in the parent's absence (hospitalization and careful monitoring may be necessary to establish this causal relationship).
- A family history of similar sibling illness or unexplained sibling illness or death. The family history also may disclose numerous medical problems that are difficult to substantiate.
- A suspected parent with an emotionally distant relationship with her spouse; the spouse often fails to visit the patient and has little contact with physicians even when the child is hospitalized with serious illness.

Supplement to *Emergency Medicine Reports*, August 7, 2006: "Apparent Life-Threatening Events (ALTE)." *Author:* **Ronald M. Perkin, MD, MA,** Professor and Chairman, Department of Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC.

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