Apparent Life-Threatening Events in Infancy

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A previously healthy 5-week-old boy who was born at term is brought to the emergency department. His mother reports that she had placed him on his side with a support pillow after breast-feeding him before she went to take a shower. Upon returning to check on him, she found him in prone position, with his nose and mouth in the mattress, "struggling" to breathe; his face was red. The mother thought he looked "sleepy." She picked him up, noting his tone was somewhat decreased; she ran his head under cold water with an increase in respiration but he still seemed sleepy.

The mother watched him for an hour and breast-fed him. After discussing it with her son's pediatrician, she brought him to the emergency department (ED).

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The infant's medical history is significant for noisy breathing (inspiratory and expiratory stridor) at 3 weeks of age. At that time, he was seen by his pediatrician and by ear, nose and throat (ENT) specialists who diagnosed him with mild laryngomalacia.

On exam, he is well-appearing, well-perfused, pink, and in no acute distress. Vital signs are all within normal range. He has mild nasal sounds transmitted to the chest, and mild intermittent inspiratory and expiratory stridor when supine and occasionally

when upright and also when sucking on his pacifier in supine position. He has no wheezing or crackles. His cardiovascular, abdominal, and neurologic exam are all normal.

APPARENT LIFE-THREATENING EVENTS

Apparent life-threatening events (ALTEs) are a common diagnosis seen in EDs across the country. ALTEs remain vaguely defined, which may be a reflection of their heterogeneous presentations and myriad associated etiologies. The commonly accepted definition is an event that is frightening and appears to the observer to be potentially life-threatening to the other, and that 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.[1]

The frightening nature of these episodes and unclear associated morbidity and mortality, coupled with the fact that many patients appear well at the time of their presentation, makes ALTEs a common management dilemma for the treating physician. In addition, while the true incidence is unknown, they may account for only 0.6% to 0.8% of ED visits for all children younger than 1 year of age, 2% of hospitalized children, and 0.5% to 6% of all infants.[2] However, one study found that in more than 12,000 patients admitted for ALTE evaluation, the mean cost was approximately $15,000 per admission.[3] In general, it presents in young infants, usually younger than 6 months of age, and associated risk factors have been reported as prematurity and positive medical history.

This article summarizes the important aspects of initial assessment, and reviews the literature on further evaluation and management of ALTEs. General pediatricians evaluating these infants in the outpatient setting may use the information and guidelines presented to determine how much concern the event should cause, and how to triage the infant appropriately. We then provide guidelines for further evaluation by ED specialists and inpatient pediatric care providers, for infants referred to the ED by pediatricians or for infants brought in directly by caregivers.

IMPORTANT ASPECTS OF PATIENT HISTORY

The most important part of the evaluation in presenting ALTEs is a thorough and appropriately tailored history. In characterizing the event, it is important not only to note the details of the event, such as length of time or appearance of the infant, but also equally important to note the environment and surrounding circumstances of the event.

For example, what was the infant doing at the time of the episode? In what position was the infant? If the child was found in bed sleeping, were the lights on or off, and therefore, what was the ability of the witnessing caretaker to describe details of the event? Or, what was the time relationship of the event to the most recent feeding? A thorough review of systems can also be helpful. Determine whether there are symptoms of upper respiratory tract infections (URTIs) that can explain altered breathing or symptoms of gastroesophageal reflux (GER) such as poor weight gain, poor intake, or arching and discomfort after feeds.

Some experts maintain that it may be important to attempt to establish the severity of the event.[4] Factors to take into account would be need for stimulation or resuscitation, and assistance provided by emergency teams.

Additionally important parts of the history include a thorough medical history. Prenatal, birth, and neonatal history can be very informative and helpful in making the diagnosis or tailoring appropriate management, as risk factors for infants requiring significant medical interventions include prematurity and a positive medical history (such as infants with a specific diagnosis such as apnea or gastroesophageal reflux).[5]

One study showed that risk factors for extreme events (eg, prolonged central apnea greater than 30 seconds; bradycardia greater than 10 seconds; desaturation greater than 10 seconds with oxygen saturation < 80%) were premature birth, symptoms of URTIs, and when infants were younger than 43 weeks post-conceptional age.[5]

Determining whether the infant is taking any medications may be helpful in further elucidating severity of and treatment for medical problems. Also of use is a thorough family history, including whether there are any family members with a history of ALTE, sudden infant death syndrome (SIDS), cardiac arrhythmias, or other causes of sudden death. A detailed social history such as whether members in the household smoke, or what the caretaker routine is, can also lend insight into risk factors for ALTE.

PHYSICAL EXAMINATION

The next important step is a physical examination. The first assessment should be whether the infant looks ill. Based on that, different pathways of management can be pursued. If an infant appears ill, concerns for serious infection and/or trauma should be foremost and the rest of the exam should be tailored appropriately. Signs of sepsis or meningitis, such as poor perfusion or neurologic impairments, may be of concern and may guide immediate steps, such as initiating antibiotics, obtaining head imaging, or taking a trauma survey.

If an infant does not look immediately ill, a more thorough exam can be undertaken. An ear, nose, throat exam and pulmonary exam can reveal upper respiratory infection symptoms. Facial dysmorphism may point to upper airway obstruction. Cardiac auscultation may reveal arrhythmia. Neurologic exam may reveal deficits consistent with trauma or abuse. A small or large head circumference or low weight may be indicative of neglect, abuse or suggest a syndrome.

WORKUP AND EVALUATION

The actual yield of workup and evaluation for ALTE remains controversial. Evaluation and workup reveals a possible etiology for ALTE in 50% of the cases.[6] In one study of ED evaluations, of 150 patients who met the definition for ALTE, 122 patients had diagnostic tests performed and only three had a positive result and only 7% had significant medical interventions performed.[4] In another study of 243 infants, the likelihood of a positive result from a single test was low (18%) and the likelihood of a result revealing the cause of the ALTE was even lower (6%).[7] Given the low yield, limited and appropriately tailored evaluation is encouraged, as there is no standard "minimal" workup for ALTE.[8]

One study of 59 infants suggested that infants aged at least 30 days old presenting with a single ALTE episode could be safely discharged from the ED without extensive diagnostic evaluation.[9] Another study of 66 infants found that laboratory evaluation was not helpful for establishing diagnosis in infants without history or examination suggestive of underlying disease or risk factors such as an earlier ALTE, unexplained infant deaths in family members, recurrent episodes, need for resuscitation, or abnormal examination.[10]

Despite the evidence that limited evaluation should be undertaken, there is remarkable variation in diagnostic strategies.[11] This may be due to poor understanding of perceived risk of disease, caregiver and/or physician anxiety, and medicolegal concerns of missing occult disease.[3]

In the clinical situation when the etiology of the ALTE is not established after a detailed history and physical examination are completed, and may be considered to be idiopathic, some clinicians advocate that a minimal diagnostic evaluation should be done, based on the low costs of tests balanced with the potential to discover a rare, yet potentially devastating disease early enough to detect long-term damage (eg, infection or metabolic disease).

> Around 50% of ALTEs fail to be explained after full workup and observation.

This evaluation would include a complete blood count, C-reactive protein, basic metabolic panel, ammonia, lactate, pyruvate, blood gas, urinalysis, toxicology screen, electrocardiogram and assessment for *Bordetella pertussis* and respiratory syncytial virus.[6]

DIFFERENTIAL DIAGNOSES

Evaluation potentially can be based on whether an event is uncomplicated versus complicated.[12] The workup for ALTE should evaluate for the following etiologies, based on the history and physical exam obtained.

Gastroesophageal Reflux

GER is a common discharge diagnosis in ALTE. In one study of 12,000 admissions, approximately 48% of infants were diagnosed with GER.[3] GER is most convincing as a diagnosis if the history includes an awake, supine infant fed in the last hour. However, establishing causality of an ALTE by GER is difficult, as research has not shown a temporal relationship between acidification and apnea.[2] Moreover, there is no gold standard for diagnosing GER. A pH probe study is considered the best test, though non-acid reflux cannot be captured; a temporal relationship may be seen, but the study does not establish causality.[13]

Upper GI series is neither sensitive nor specific.[3] One study of 313 patients admitted for ALTE found a discharge diagnosis of GER in 49% of the cohort. Although these patients were largely well-appearing on hospital presentation, they were more likely to have received rescue breaths by their caregivers than for other diagnoses, suggesting that subjective "severity" of the event may be uninformative. Few of these admitted patients had events during hospitalization, and there was a low rate of diagnostic testing or specialty consultation. However, 9% had recurrent ALTE events at 6-month follow-up. Overall concordance of working diagnosis of GER to discharge diagnosis was very high at 96%.[14]

Another study found that infants admitted with ALTE had very few adverse outcomes, defined as aspiration pneumonia, failure-to-thrive, or anti-reflux surgery, associated with a diagnosis of gastroesophageal reflux disease (GERD). However, almost 12% of these patients had readmission for a second ALTE, which is much higher than for all ALTE diagnoses.[15]

Respiratory Infections

Most respiratory causes are related to infections, though central and obstructive sleep apnea can occur in isolation, especially in premature infants. Infectious etiologies associated with ALTEs are myriad. The most common

culprits are lower respiratory infections, including bronchiolitis or pneumonia, accounting for approximately 20% to 30% of discharge diagnoses.[3] Respiratory syncytial virus has been shown to cause apnea, though the pathophysiology is poorly understood.[2] Upper respiratory infections such as pertussis can also be considered with a consistent history and physical exam. A chest radiograph can be obtained, as indicated by history and physical examination. While bacterial meningitis, sepsis, and urinary tract infection account for approximately 9% of the diagnoses, they should be considered in an ill-appearing infant.[3] Viral and bacterial evaluation should be tailored according to history and examination findings.

Neurological Issues

Neurologic problems, including seizures, appear to account for approximately 10% to 20% of ALTEs.[16] In one study, electroencephalogram (EEG) had a sensitivity of only 15% for diagnosing epilepsy.[17] Of the almost 4% of infants presenting with ALTE and who developed chronic epilepsy, 71% had a recurrent ALTE within 1 month and almost half were diagnosed with seizures in the week after presentation,[17] leading some to suggest that EEG should be performed on those with recurrent ALTE.[6]

Cardiac Concerns

Cardiac arrhythmias are rare in children, accounting for approximately 5% to 10% of discharge diagnoses. Cardiac dysrhythmias may be associated with sleep apnea. Some studies have reported very high rates of cardiac arrhythmia in full-term and otherwise healthy infants with previous ALTEs on 24-hour continuous Holter monitoring, including prolonged corrected QT interval, premature ventricular or atrial beats, or sinus node irregularity.[2]

Other Concerns

When appropriate for the medical history, physical exam, or laboratory or radiologic examinations, other rare causes that should be considered include metabolic causes, ENT abnormalities (such as laryngeal or tracheal abnormalities), ingestions, and/or Munchausen-by-proxy. Many metabolic conditions are triggered by fasting and may be accompanied by symptoms of hypotonia, lethargy, or vomiting.[8] In these cases, laboratory evaluation, including blood glucose, pH, ammonia, lactate, and pyruvic acid levels, may be helpful.

Child Abuse

Child abuse is also in the differential diagnosis and should always be considered because the mortality associated with child abuse is high. In one study of 243 infants with ALTE, 2.5% were diagnosed with abuse-related head injury, and while mortality for all ALTEs was 1.3%, mortality from ALTEs presenting with abuse was 33%.[18]

Historically, it is well-known that infants with head injuries may initially appear well. One study in 2008 found that in four of their cases of nonaccidental trauma causing ALTE, three of four children had a suspicious history; all four had physical findings (specifically, skin and/or neurologic findings).[19]

Other factors that have been identified that may suggest abuse include recurrent ALTEs, previous SIDS (especially at late ages), fresh blood found in the nose or mouth, delay in seeking medical care, a confusing or changing history as given by caregivers, and failure to respond without vigorous resuscitative efforts.[4] If there is a suspicion of abuse, the evaluation should include ophthalmologic exam for retinal hemorrhage, head computed tomography (CT), and skeletal survey.[19]

In another study, 2% of 563 patients presenting with ALTE were diagnosed with child abuse, and one of these 11 children died. The other two children in this study died of SIDS, according to the autopsy.[20]

ALTEs used to be referred to as "near-miss" SIDS in the past, though now it seems that these represent distinct entities. While they do share some overlap in risk factors, ALTEs usually occur in infants younger than 2 months old, while SIDS peaks at 2 to 3 months of age, and up to 50% of ALTEs occur in awake infants, while SIDS occurs when infants are sleeping. In the past 20 years, the incidence of SIDS has decreased with the National Institute of Child Health and Human Development's Back-to-Sleep initiative, whereas ALTE incidence has remained the same.[16] Despite all these possible diagnoses, around 50% of ALTEs fail to be explained after full workup and observation and are thereafter labeled "idiopathic."[6]

MANAGEMENT OF ALTE

Hospitalization

After an ALTE workup, hospitalization of an infant is required if the etiology appears to be life-threatening. In a systematic review, McGovern and colleagues[21] suggested in an algorithm that an infant be hospitalized for a minimum of 24 hours with cardiorespiratory monitoring if the ALTE is not described as a first, short, self-correcting episode associated with feeding.

If history and examination are not helpful in determining a cause, baseline investigation and possible subspecialist referral during hospitalization can be undertaken.[21] A study of neonatal and pediatric intensive care unit admissions for ALTE found that for 88 infants admitted for severe ALTE, the mortality was much higher (approximately 15%) than for all infants presenting with ALTE.[22]

In contrast, a study of 59 infants 1 year old or younger suggested that only

14% of patients evaluated in the ED for ALTE had a condition or subsequent event requiring hospitalization. All of these met high-risk criteria, which were multiple ALTEs within 24 hours or up to 1 month of age, suggesting that infants older than 1 month of age who experience a single ALTE are low risk and can be safely discharged from the ED.[9] Another study of 300 infants evaluated for ALTE in the ED proposed a clinical decision rule to identify infants who are safe to discharge home from the ED. These investigators found that prematurity, abnormal physical exam in the ED, color change to cyanosis, absence of URI symptoms, and absence of choking during the episode predicted need for significant intervention.[23]

However, even in cases where no immediately serious etiology can be found or risk factors identified, hospitalization is often used because of caretakers' anxiety and physician discomfort with the poorly understood morbidity and mortality. Hospitalization may also be helpful to further navigate around social or family issues. For example, if there is concern about noncompliance, hospitalization may be required to allow for workup and essential diagnostic testing before the treating physician feels reassured that the infant will be safe at home.

In cases of suspected but unclear child abuse, the family's interactions with the baby can be monitored in the hospital setting. Additionally, social services can be consulted to help further evaluate the caretakers.

In some cases where the medical cause is unclear and history and presentation are of enough concern, in-patient consultation can be helpful. Gastroenterology can help guide appropriate imaging, such as swallow studies, or upper gastrointestinal series. Neurologists can guide imaging or EEG monitoring. Pulmonologists may suggest polysomnography, which may be enlightening because research on infants with ALTE suggests altered sleep patterns.[24] Furthermore, obstructive sleep apnea can be found in association with respiratory infections, allergies, sleep deprivation, anatomic abnormalities, and can be potentiated by some medications. It can also be idiopathic in young infants, especially those with a history of prematurity.[8] Cardiologists may guide EKG or Holter monitoring.

> Early identification may result in more timely intervention and prevent prolonged or more serious and/or prolonged hypoxia and complications.

The high costs and low yield of these tests should be carefully weighed when considering involvement of a specialist and obtaining these studies.

Individualized Treatment

Outside of hospitalization, the key aspects of ALTE management are individualized evaluation and follow-up. After the diagnosis is made, it is important to treat the underlying etiology. It is also important to educate the families. For example, families should be informed about safe sleep practices, including supine sleep, and the dangers of tobacco smoke exposure.[8] In some situations, caretakers should be taught basic life support, depending on etiology of the ALTE and parent/caregiver wishes. Lastly, caretakers should be warned of the negative effects of shaking infants at any time; in one study, 33% of caretakers reported shaking the infant after the ALTE.[25]

Home Monitoring

Historically, some researchers have suggested that home monitoring may protect infants at higher risk for SIDS, though there is not good evidence to support this.[8] There are no universal criteria available to determine which infants should be sent home with monitoring. High-risk patients may be those with documented sleep apnea, airway anomalies, or technology-dependent infants, such as those requiring oxygen at home or with tracheostomy. One study showed that home monitors alerted caregivers to illness in many monitored premature infants admitted with ALTE.[22] Early identification may result in more timely intervention and prevent prolonged or more serious and/or prolonged hypoxia and complications.[4]

Importance of Follow-Up

No matter what the discharge plan, it is essential to ensure good follow-up with the child's primary pediatrician. One study of 471 patients with ALTE followed for an average of 5.1 years, showed two deaths, both related to chronic respiratory problems and bulbar insufficiency associated with underlying seizure disorder and severe developmental delay.[17] In almost 5% of patients, adverse neurologic problems developed, including chronic epilepsy or developmental delay.

Moreover, in these patients, in-patient neurologic examination had a low yield for predicting long-term adverse neurologic outcome. These patients were also found to be at high risk for presenting again within 1 month of their initial ALTE. In addition, whereas the etiology of the ALTE was identified as being secondary to abuse during the initial evaluation in two patients, abuse was subsequently identified in 52 other patients, suggesting that this group of families be followed as "high-risk" families.[17]

CONCLUSION

ALTE is a confusing entity, representing a constellation of descriptive symptoms and signs; it is not a diagnosis. Multiple possible etiologies and difficulties in evaluating and managing infants presenting with these events is a challenge for primary care physicians, ED specialists, and subspecialty pediatricians. The evaluation of these infants should include a detailed history and appropriate physical examination and diagnostic testing guided by clues obtained from the history and physical examination.

There is no real consensus on minimal diagnostic evaluation and what history and risk factors exactly should lead a practitioner toward admission or discharge from the ED in infants who present with ALTE who do not appear acutely ill. Clinical judgment remains a very important part of the decision-making process. ■

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