Apparent Life-Threatening Events: An Evidence-Based Approach

An ambulance arrives at the ED with a 10-week-old male who stopped breathing at home. The boy's mother notes that she had just put him down to sleep in his crib; when she went to check on him about 15 minutes later, he was blue and not breathing. She quickly picked him up and tried calling his name and rubbing his back in attempt to awaken him. When that failed, she attempted mouth to mouth resuscitation and chest compressions. The boy's father heard mom's screams, rushed to the baby's room, and quickly activated Emergency Medical Services (EMS). Upon EMS arrival, the baby was awake and breathing on his own and in no apparent distress.

The baby arrives at the ED via ambulance. He is triaged and placed in a room on a cardiorespiratory monitor. After a quick assessment, you concur with the triage nurse's evaluation and begin to gather more history. The baby was born at term, vaginally, after an uncomplicated pregnancy, delivery and post-partum period. The baby fed well while in the nursery and was discharged home with mom on the second day of life. The baby has done well since leaving the hospital. He is growing well, with weight, length and head circumference all at the 75th percentile.

The baby is formula-fed and has only had rare episodes of reflux. There has been no history of fever, upper respiratory tract (URI) symptoms, cough, vomiting or diarrhea.

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The baby is on supplemental vitamins only. Family history is negative for childhood deaths or congenital cardiac abnormalities. The baby has no siblings and lives at home with his parents. He is not in daycare. There are no other care providers.

Editorial Board

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CME Objectives

- Upon completing this article you should be able to:
  1. Identify patients meeting the definition for an ALTE.
  2. Identify the common etiologies of ALTEs.
  3. Discuss the controversies regarding the Emergency Department evaluation of patients after an ALTE.
  4. Discuss the controversies in the relationship between ALTE and SIDS.

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See "Physician CME Information" on back page.
The baby’s vitals are as follows: temperature 36.8, pulse 138, respiratory rate 32, blood pressure 92/55, and pulse ox of 100% on room air. While you examine the baby, he is feeding eagerly from a bottle. The physical examination is entirely unremarkable.

You decide that the patient has had an Apparent Life-Threatening Event (ALTE). The ED is quite busy and his nurse is asking for orders and for the anticipated disposition. Several issues come to mind as you consider your response.

- What are the possible etiologies of this event?
- What is the role of infection in an ALTE?
- Is it just gastroesophageal reflux?
- Should I admit this patient?
- Does this patient need to be discharged on a cardiorespiratory monitor?

The mere mention of an ALTE necessitates disagreement and confusion. The term itself developed through an attempt to provide a name for this clinical entity without suggesting an etiology. Old terms included many variations of such phrases as near-miss SIDS, near-miss cot-death, attacks of lifelessness, and prolonged infant apnea. Confusion continues with the history which is often obtained from a caregiver who is convinced that the child’s life was at risk. Answers to questions regarding the duration of the event, limb movements, skin color, apnea, and the effect of resuscitative measures may be misleading simply due to the frightening nature of the event. It is difficult to say how much of the caregiver’s history should be taken at face value. The physical examination is also associated with some controversy.

In this article, the following questions will be addressed. Does a significant abnormality in the physical examination immediately exclude the diagnosis of ALTE? What diagnostic testing is important, and can the same tests be used in every case? Where should the baby go after ED evaluation; should they be monitored on an inpatient or outpatient setting? Should they be monitored at all?

Many of the confusion and controversy regarding ALTE lies in the heterogenous nature of these patients. In fact, the most commonly utilized definition for ALTE generates dissent among researchers and care providers. This definition was established at the 1986 National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring. Ironically, this conference itself was assembled as a result of the ever-increasing controversies in Sudden Infant Death Syndrome (SIDS) research in general, with particular attention to ALTEs and the role of home monitors. In the consensus statement from this summit, the following definition for an ALTE was offered: “an episode that is frightening to the observer, that is characterized by some combination of apnea (centrally 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 feels that the infant has died.”1

While this definition may seem to capture the essence of an ALTE, its application presents considerable difficulties. All of the following vignettes are examples from the literature. Which of these scenarios should be considered an ALTE?

1) A 4-week-old male infant who was initially seen for a chief complaint of limpness associated with shallow breathing.2
2) 2-month-old girl with repeated cyanotic episodes during ED evaluation.3
3) An 8-month-old boy who presented with respiratory distress, wheezing, cough, and a sudden episode of apnea … had hyperinflation on chest radiograph and a positive RSV antigen test.4
4) A 9-week-old boy with a 10-second episode of limpness and cyanosis.4

Scenario 4 would likely have the greatest consensus in its designation as an ALTE. Few would argue that an infant with an episode involving a change in tone and color should not be an ALTE. In actual fact however, all four cases have been selected from manuscripts in which they met their respective definitions for an ALTE. This example typifies some of the difficulties presented by the NIH Consensus definition.

The NIH Consensus definition on its own is probably inadequate as a means to identify patients for selection in a study. The definition lacks precision and clarity in a number of areas. No age range is provided. No criteria exist for the symptomatology necessary to classify an episode as an ALTE. For example, consider a scenario whereby a parent is feeding a young infant who then starts to cough and choke on the formula. The baby gags, turns red and the parent becomes alarmed and administers back blows. This would meet the NIH Consensus definition for an ALTE. This event however is probably best classified as a choking episode. A second diagnosis for this patient is not likely to be clinically useful or meaningful. This patient should probably be...
evaluated and treated much differently than the patient who had an apneic and cyanotic episode. Through the use of the NIH Consensus definition alone, one cannot make such distinctions.

The NIH Consensus definition also makes no allowance for the clinical presentation of the patient after the ALTE. If one were to reconsider Scenario 3 on the previous page, they would determine that the baby certainly met the NIH Consensus definition criteria for an ALTE. However, another approach would be to consider that this patient already has a clearly defined disease process, namely respiratory distress (and possibly respiratory failure) from respiratory syncitial virus (RSV) bronchiolitis. Again, the utility of an additional diagnosis of ALTE is debatable and probably adds little to the management of this patient.

Investigators have taken various approaches with regards to the clinical presentation of patients with the diagnosis. Some have argued that the diagnosis of ALTE should be reserved only for those who are well appearing at the time of their presentation to medical care. Others have been less rigorous in their approach, noting that patients are often well-appearing by the time they present to medical care. Brand et al have employed the unique approach of dividing ALTEs depending upon whether the history and physical examination findings suggest a cause.

Clearly, there is a wide range of opinions in how to determine what is an ALTE and what is not. While the debate over what exactly constitutes an ALTE continues, pay careful attention to the study definitions when interpreting the literature. The results of any work are undoubtedly influenced by the researchers’ interpretation of the term ALTE.

Clinical Appraisal of the Literature

While the literature regarding SIDS is vast, the volume of literature relating to ALTE is considerably less. A substantial amount of literature regarding the etiology, diagnosis and evaluation of ALTE exists and is usually in the form of case reports, case series, reviews, consensus statements, and meta-analysis. There are a small number of retrospective and prospective studies. No randomized clinical trials exist. The data regarding the role of gastroesophageal reflux, while less applicable to the ED setting, is of better quality and includes prospective studies.

Epidemiology

The true incidence of ALTE remains unknown. Estimates from studies conducted in the 1980s range from 0.46-10.0 per 1000 live births. One large prospective study performed in western Austria from 1993-2001 found an incidence of 2.4 per 1000 live births. While the rate of SIDS was noted to drop during the study period both within the study group and elsewhere, there was no similar pattern for ALTEs. The average age for patients with an ALTE is younger than that for SIDS. In one recent prospective study, the average age for an ALTE was 8 weeks of age, compared to 18 weeks in SIDS. Others have reported similar data in a case-control study.

SIDS is defined as “the sudden death of an infant under 1 year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.” Risk factors that place infants at risk for SIDS have long been established and are extensively documented. A recent review by Hunt and Hauck documents this. The list of risk factors includes a peak in the winter months, male gender, prematurity, low birth weight, poverty, young maternal age, single parenthood, poor prenatal care, higher parity, multiple gestation, smoking (during and after pregnancy), drug and alcohol use, and prone or side sleeping positions. Recently, there has been some focus upon the use of pacifiers and bed-sharing although these issues are more controversial. Education campaigns focusing upon the benefits of a supine sleeping position are credited with a significant decrease in the incidence of SIDS.

The risk factors for ALTE are not as clear. From the limited available data, it appears that the majority of risk factors for SIDS are not predictive for an ALTE. There may be, however, some association of ALTE with maternal smoking. Upper respiratory tract infections are known to prolong apneic episodes and may be an independent risk factor.

Etiologies

The number of potential etiologies for ALTEs is vast. A list of more frequently reported conditions that may cause an ALTE is shown in Table 1 on page 4. The more important etiologies will be reviewed.

Cardiac

In older children and young adults, sudden unex-
expected death is often due to cardiac causes. The list of pathologic states includes myocardial abnormalities, congenital structural malformations, rhythm disturbances and anomalies of coronary vessels. Cardiac pathology has also been identified in cases of presumed SIDS. Approximately 10% of patients with sudden unexpected death have underlying cardiac etiologies. However, this study included patients with known cardiac abnormalities. Structural lesions were present in the majority of cases. Cardiac pathology should be given strong consideration in cases where death occurred while the patient was awake.

Cardiac pathology has been identified in ALTEs. It is uncertain as to whether structural lesions are in the majority as in cases of infant death. Although structural lesions may cause an ALTE, lesions leading to cyanosis are often dependent on a patent ductus arteriosus and often manifest in the neonatal period. In some instances, these infants will present in shock several weeks after birth.

More data exist regarding the role of dysrhythmias in ALTEs. Early cardiorespiratory monitoring studies of infants after an ALTE noted some cardiac arrhythmias. In a series of 8 patients undergoing monitoring after an ALTE, seven were noted to have significant cardiac arrhythmias. The rhythm changes occurred during episodes of sleep apnea. All infants had episodes of bradycardia. Seven of these patients had at least one sinus node arrest lasting 2-5 seconds. One infant had a bradycardic episode that was immediately followed by shift to a nodal rhythm, widening of the QRS complex and flattening of the T-waves. The infants in this study were not treated for these arrhythmias. None of the infants had any sequelae at 6 months of age. Follow-up was available for 7 of the 8 patients between 4 and 7 years of age; it too was unremarkable.

Larger series have identified dysrhythmias in association with ALTE. In a series of 100 full term healthy infants who had an ALTE, 24-hour continuous cardiograms (Holter) were abnormal in 62% of patients. Premature ventricular depolarizations (25%), prolonged QT (30%), premature atrial depolarizations, and sinus node irregularity (39%) were among the rhythm disturbances reported. No cases of supraventricular tachycardia, ventricular tachycardia, or atrioventricular block were noted. Only two patients with sinus node dysfunction required treatment and all patients did well in follow-up. Another study showed a wider QT-dispersion (difference

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between the maximum and minimum QT interval across the 12 leads) in infants after an ALTE compared to the control group.23

The link between Long QT syndrome and SIDS has received much attention. In particular, there was hope of uncovering a genetic marker for SIDS. While there has been extensive effort to identify a genetic defect for SIDS, it appears more likely that there are a series of genetic defects that cause or, under certain circumstances, have the potential to cause SIDS.24 There are only 2 reported cases of ALTE where a prolonged QT interval resulted in either torsade-de-pointes or ventricular fibrillation in which a causative genetic marker was identified.25, 26 The clinical implication of prolonged QT interval and its link to ALTE and SIDS remains unclear.

Gastrointestinal

A number of both acute and chronic conditions of the gastrointestinal tract may cause an ALTE. Common acute abdominal pathologies including volvulus, intussusception, strangulated hernia and infection have been associated with ALTE.6,7,27,28 More interesting, however, are discussions and speculation about the role of gastroesophageal reflux and the laryngeal chemoreflex.

Gastroesophageal reflux is usually considered physiologic in neonates and young infants. Symptoms tend to improve during the first year of life. In severe cases it can cause esophagitis, bleeding, poor growth, and pulmonary aspiration. Gastroesophageal reflux was first associated with apnea in the mid 1970s.29,30 Years later, gastroesophageal reflux was identified in 13 of 15 patients with a history of apnea while awake and was not detected in a control group.31 Esophageal pH monitoring in 8 of 34 infants after an ALTE showed evidence of reflux.32

Many studies of ALTEs include gastroesophageal reflux as a common etiology, citing it as the cause in 18-66% of cases.5,7,28,33 Infants with severe gastroesophageal reflux are known to have episodes of irregular breathing.34 Medical and surgical treatment of reflux has been shown to decrease apneic episodes.35 Acids placed in the esophagus has induced apnea in an animal model.36 However, since gastroesophageal reflux has been noted in approximately 67% of 4-month-old infants the clinical significance of reflux, even that noted in medical imaging studies, is debatable.37

It is a common presumption that the episode of reflux is the trigger for the ALTE. In a group of 67 patients with a history of an ALTE, the temporal relationship between these two phenomena was investigated. In this group, 35 patients (52.8%) were found to have reflux. In 14 of the patients with reflux, their symptoms at night were so severe or frequent that a temporal relationship could not be established. In the remaining 21 infants, esophageal pH, cardiopulmonary monitoring, limb activity, and electroencephalogram were monitored overnight. Over 700 apneic episodes were recorded. Only 19% of the apneic episodes were coupled with reflux and the apnea preceded the reflux in over 90% of the instances.

The limitation of an esophageal pH probe for the detection of reflux is that it will not capture non-acid reflux. Investigators have combined multichannel intraluminal impedance monitoring and esophageal pH measurements to capture both episodes of acid and non-acid reflux.39 In a prospective study of 25 infants with ALTE or apnea, 527 total apneic episodes were captured. Only 80 cases (15.2%) were temporarily linked to gastroesophageal reflux. Of these, approximately half were associated with acid reflux; the other half with non-acid reflux. Again, the temporal link between apnea and gastroesophageal reflux could not be established.

The supine sleeping position is known to increase gastroesophageal reflux. The recommendations of supine sleeping for infants and its correlation to a decrease in the incidence of SIDS works against gastroesophageal reflux as a mechanism for SIDS and perhaps apnea.

The laryngeal chemoreflex has been proposed as a mechanism for ALTE and SIDS. It has been well-described in tracheostomized animals and is triggered by direct fluid stimulation of the laryngeal mucosa. The larynx can be stimulated by instilling fluid directly through the tracheostomy or from fluid in the pharynx. What results is a complex series of reactions that include apnea, bradycardia, swallowing, and hypertension.40 This reflex appears to be present only in young infants.41

This mechanism has been tested in healthy neonates in both the prone and supine position.42 Physiologic changes on 10 asleep infants were made before and after instilling 0.4mL of water into the oropharynx via feeding tube. In the 10 sessions, 164 infusions were made with 96 during active sleep (48 supine, 48 prone) and 68 during quiet sleep (28 supine, 40 prone). The most frequently noted
responses were swallowing (95%) and arousal (54%). There was a significant reduction of swallowing and breathing when patients were in the prone position. This suggests that airway protection is compromised in the prone sleeping position.

**Airway/Respiratory**

Apnea is a pause in inspiratory gas flow. The duration of the pause necessary to diagnose apnea will vary among different investigators but is typically longer than 15 (or 20) seconds. Some suggest that the duration may be shorter if there is associated pallor, cyanosis or bradycardia. Apnea may be central or obstructive; this distinction is based upon the inspiratory effort. In central apnea, there is no inspiratory effort. These are central nervous system disorders and are uncommon. During obstructive apnea, there is continued respiratory effort. The apnea is due to some form of airway obstruction. Adenotonsillar hypertrophy is a common example. Occasionally there are features of both obstructive and central apnea; this is considered mixed apnea.

Abnormalities of the upper and lower respiratory tract are common causes of ALTEs. However the pathology is usually due to a respiratory pathogen. Congenital anomalies or other causes of airway obstruction are much less frequent.

RSV is an extensively documented cause of apnea. Early data suggests that approximately 20% of hospitalized infants experience apnea secondary to RSV infection. The apnea may be a result of respiratory distress, failure due to bronchiolitis, or simply the result of the RSV infection itself. Infants less than two months of age may be at greater risk for apnea.

Other respiratory pathogens may cause an ALTE. Pertussis infection is also a well-known cause of ALTE. Particularly in young infants, the symptoms may be more subtle. The patient may have the “staccato” cough or simply present with apnea. The classic “whoop” may not be present. This infectious etiology is often overlooked and may be a co-infection with RSV. Chlamydia infections are less frequent but are also known to be a cause of ALTE.

Numerous structural lesions of the respiratory tract are noted to cause ALTE. One study noted anomalies in the pharynx (adenotonsillar hypertrophy), the larynx (laryngomalacia, edema, subglottic ductal cyst, subglottic stenosis), or the trachea (tracheomalacia, aberrant innominate artery). This study may have been subject to some referral bias as all patients in this series were referred for otolaryngology evaluation after and ALTE. Foreign bodies may also be responsible for an obstructive process.

A number of studies have attempted to elucidate a physiological explanation for ALTE. One study compared diaphragm muscle strength in a group of patients with a history of ALTE to a group of controls. Patients with a history of ALTE had equal or better diaphragm strength as compared to controls. Another study noted that surfactant samples obtained via bronchoscopy were more frequently abnormal in patients with history of ALTE as compared to controls. However, some of the control patients had similar abnormalities and thus the clinical importance of this finding is unclear. Pulmonary function tests on a group of patients after an ALTE showed a significant reduction in the median maximal flow at functional residual capacity. This measurement is considered a sensitive indicator of small airway patency. Despite these findings, an explanation for ALTE based upon pulmonary pathophysiology remains elusive.

Another approach to providing evidence for a mechanism was an investigation regarding sleep-disordered breathing in infants with an ALTE and their families. This large study included 348 patients with a history of ALTE and their parents, siblings and grandparents. The infants and controls (usually siblings of SIDS victims) had a complete sleep evaluation that included interviews with caretakers, reconstruction of the sleep/wake behavior for the previous three days and a questionnaire addressing breathing and movements while asleep and behavior while awake. All children had a physical examination of the face and oropharynx and nocturnal polygraph readings. Adults were also questioned with regards to their sleep patterns and had a general physical examination as well as a detailed craniofacial evaluation. Approximately 57% of patients with ALTE history had sleep-disordered breathing (abnormal breathing patterns that disturb sleep). In this group, 43% of family members had been treated for sleep-disordered breathing compared to 7% in controls. Treatments for sleep-disorder breathing included nasal CPAP, or surgical/dental appliances. The results imply that the same genetic factors that are responsible for small upper airways can cause ALTE in infants and sleep-disordered breathing in adults.

**Infectious**

Apart from the respiratory pathogens noted above, a
small number of patients will have a bacterial etiology for the ALTE. The question of which patients need an evaluation for sepsis poses a significant clinical challenge, particularly in neonates and very young infants. The number of patients with bacterial meningitis or bacteremia/sepsis is very low, much less than 1% as noted in a recent systematic review. There is no data regarding the risk of meningitis in well-appearing, afebrile infants with an ALTE.

Urinary tract infection (UTI) is believed to be a more common etiology with one series reporting it as the cause of ALTE in 8% of patients. Numerous studies of ALTEs however, fail to identify UTI as the cause for any of their patients. A careful physical examination and a period of observation may help identify those patients at risk for bacterial infection. There is some data suggesting that prematurity may be a risk factor.

**Neurologic**

Seizures are the most common neurologic disorder to cause an ALTE; however, the proportion of patients with an ALTE that are diagnosed with seizures is unknown. Many studies report a rate of 3-7%; one study noted a rate of 25%. A number of other non-traumatic neurologic diagnoses may cause an ALTE.

Congenital central hypoventilation syndrome (Ondine’s curse) was first described in 1970. In this disorder, there is a failure of autonomic control of breathing in the absence of cardiac, pulmonary, neuromuscular, or brainstem pathology. Patients lack a central chemosensitive response to hyperpnea and have no ventilatory response to hypoxia. In some cases, the hypoventilation is limited to sleep. However, in severe cases there is hypoventilation in both asleep and awake states. This order is extremely rare, with estimates of about 300 affected children worldwide. Diagnosis involves sleep studies and a thorough evaluation to rule out other neurologic or metabolic abnormalities. Other neurologic etiologies include brain tumor, hydrocephalus, neuromuscular disorders, vasovagal reactions, and congenital malformations of the brain.

Breath-holding spells have been identified as a cause of ALTEs. These episodes are usually associated with cyanosis. On rare occasions there is pallor instead. These patients are typically older than those having an ALTE. A careful history often reveals that the episodes were preceded by a sharp cry or painful experience.

**Metabolic**

Inborn errors of metabolism have been noted in families with a history of SIDS and ALTE. The frequency of this group of disorders has been estimated to be approximately 7.7% in one study. In this study, 65 patients referred for apnea were retrospectively evaluated. All of them had complete metabolic evaluations. Patients with an inborn error of metabolism seemed to have some important differences compared to those having an ALTE without a metabolic defect. Those patients with a metabolic disorder were more likely to have a family history of SIDS, hepatomegaly on physical examination, resuscitation or vigorous stimulation to resolve the event, and recurrent events. Disorders of fatty acid oxidation and urea cycle disorders were identified most commonly. While the number of patients in this study was small, these factors may be helpful clues in making what is often a challenging diagnosis.

Electrolyte disorders are another etiology for ALTE. Hypoglycemia, hypocalcemia, and hypomagnesemia have been reported, but such disorders are quite rare.

**Injury and Ingestion**

Nonaccidental trauma is a difficult but necessary consideration when evaluating a child after an ALTE. One should remember that this diagnosis will apply in only a small number of cases and that the role of the physician is not to identify those responsible for inflicting the injuries. Once the appropriate authorities have been alerted to the possibility of non-accidental trauma, the physician maintains a role limited to that of healthcare provider.

A careful history and physical examination may yield clues regarding this diagnosis; however, even in cases of significant head trauma, there may no physical findings. A recent study of infants referred for child abuse investigation identified 19 infants with a subdural hematoma on computed tomography (CT) or magnetic resonance imaging (MRI). Eight patients had retinal hemorrhage as well as other traumatic injuries and were victims of abuse. Two patients had small subdural hematomas associated with accidental linear skull fractures. The remaining infants had no signs of trauma apart from that noted on imaging. Inflicted injury was diagnosed in eight of these patients and possible inflicted injury was the diagnosis in the other child. Retinal hemorrhages have been detected in patients after an ALTE prompting some to consider a fundoscopic
examination a routine component of the evaluation of an ALTE.2

Intentional suffocation is a known etiology in ALTE and “presumed SIDS” cases. The exact incidence is unknown but one study documented intentional suffocation in 18 of 157 patients being monitored at home or in the hospital for apnea.59 There is some limited evidence that the following set of circumstances are concerning for intentional suffocation:60

- Previous recurrent cyanosis, apnea, or ALTE while in the care of the same person
- Age at death older than 6 months
- Previous unexpected or unexplained deaths of one or more siblings
- Simultaneous or nearly simultaneous death of twins
- Previous death of infants under the care of the same unrelated person
- Discovery of blood on the infant’s nose or mouth in association with ALTEs

Munchausen syndrome by proxy is a dangerous form of child abuse. Early descriptions of the disease included four important elements. The illness of the child is simulated and/or produced by a parent or someone acting in loco parentis. There is repeated presentation of the child for medical care. The perpetrator denies knowledge regarding the cause of the child’s symptoms. The symptoms resolve when the child and perpetrator are separated.61 The term “factitious disorder by proxy” has been proposed as the label for a psychiatric condition for the individual who deliberately simulates or induces illness in a child to fulfill psychological needs.62 “Pediatric condition falsehood” is a term with similar implications.63

Poisoning of infants can be intentional or unintentional. Medication errors are quite plausible. Many substances, including opiates and cocaine, have been inadvertently passed to infants via mother’s breast milk.64, 65 These scenarios should not be particularly concerning for abuse. Intentional poisoning, however, can be responsible for an ALTE. The first report of this phenomenon was a case series stimulated by a mother’s admission of giving her child methadone since she was concerned that her child was experiencing narcotic withdrawal.66 The infants in this case series were noted to be younger than the usual age for ALTE, and were reported to be fussy before the event. Many of these infants had significant physical examination findings that included prolonged changes in tone (stiff or hypotonia), lethargy, or recurrent events. While this series was small (9 patients), these factors may be important considerations for this diagnosis.

Hematologic

Through a variety of proposed mechanisms, anemia and subsequent transfusion has been shown to change respiratory status in premature infants.67 In one study, 34 of 41 infants being evaluated for an ALTE, the hemoglobin level was below normal values.68 Recently a prospective study compared hemoglobin levels in patients with recurrent ALTE, those with a single event and controls.69 Patients with recurrent events had a higher rate of anemia (21.6%) compared to those with a single event (16.9%) and the controls (9.5%). The mean hemoglobin levels in these three groups were 11.6 g/dL, 13.1g/dL and 12.9 g/dL respectively. It is unclear how these small but significant differences in hemoglobin levels manifest themselves as either an ALTE or recurrent ALTEs.

Idiopathic and Other Causes

Numerous case reports describe other causes of ALTE but they are certainly very infrequent and their clinical usefulness is probably limited. Many patients however will have no identifiable cause of their ALTE. The rates will vary; a recent systematic review noted that an unknown cause was noted between 0 and 83% of cases, depending upon the study.52 This number will depend upon the definition that investigators in any particular work use for an ALTE, thoroughness of the diagnostic evaluation, and their clinical interpretation of the finding or diagnosis of gastroesophageal reflux. Outcome data for this group of patients in particular, is lacking.

Emergency Department Evaluation

Clinical Presentation

Patients are often well-appearing after an ALTE at the time they present to medical care. This may not always hold true as the definition of ALTE can be interpreted in many ways. The patient may have an obvious etiology or may have recurrent events while in the ED. This variability in clinical presentation has also been noted in the pre-hospital setting.70

History and Physical Examination

There are several goals of the ED evaluation of patients after an ALTE. As always, a rapid cardiorespiratory assessment is needed to rule out the need
for immediate life-sustaining interventions. The rest of the evaluation should focus on two issues. First, decide if the episode was truly an ALTE or if the process was more benign. Second, determine the likelihood of an etiology that requires urgent or even emergent treatment. Given the wide scope of etiologies, this presents a significant clinical challenge.

The importance of a thorough history and careful physical examination cannot be overemphasized. Abnormalities in these areas have been correlated with establishing a definitive diagnosis, relative risk 3.8 (95% confidence interval 1.6-9.3).7 The history of the event itself should focus upon a number of issues. These are summarized in Table 2. Cyanosis and apnea are the most common presenting symptoms.7 One should remember that these events are, by nature, very frightening and some details could be inexact. The physical examination should be thorough and include vital signs and pulse oximetry. A normal physical examination, however, does not exclude significant underlying pathology.

The ED diagnostic evaluation of infants after an ALTE is extremely controversial. The differential diagnosis of ALTE is quite large and testing for all possible etiologies is not feasible. Evidence-based guidelines do not exist nor does the presence of an abnormal test result indicate causality. A recent consensus document noted that “there is no standard minimal work-up in the evaluation of an ALTE”.71

Several studies have addressed the question of the appropriate ED evaluation of these infants. All patients presenting to a Pediatric ED after an ALTE were reviewed retrospectively for a one-year period.6 In the study timeframe, there were 130 patients with a total of 196 apneic episodes. Patients were selected based upon ED discharge diagnoses. The most commonly performed diagnostic tests included urinalysis, chest x-ray and “blood tests” (blood count and chemistries). Chest x-rays were most likely to be positive. These were performed in 34% of ALTEs and 28% were abnormal. Blood tests were performed in a similar number of cases and were abnormal in 17% of patients. However, the abnormalities were considered mild (usually mild hyponatremia, mild hypokalemia or leukocytosis) and did not alter management. Urinalysis was abnormal in 7% of cases although only 1% of patients were diagnosed with urinary tract infection.

Another study retrospectively reviewed 150 patients over a 5-year period.3 Patients were identified based upon a review of the chief complaint logs. The study considered significant medical interventions based upon diagnostic tests ordered in the ED for patients after an ALTE. In only three patients did testing result in a specific intervention. One patient

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<th>Table 2: Important Issues to Address in the History after an ALTE</th>
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Clinical Pathway for Patients After An ALTE

Chief complaint consistent with ALTE

Stable cardiorespiratory status?

YES

History and physical exam suggests ALTE

NO

Benign process?

YES

Observe, anticipate discharge (Indeterminate)

NO

Reassess working diagnosis

NO

Positive clinical findings?

YES

Consider limited diagnostic evaluation (Indeterminate)

NO

Diagnostic evaluation based upon clinical findings. (Class II)

NO

Admit (Class III)

Stabilize patient. Continued cardiorespiratory support necessary?

NO

Finish history and physical examination (Class II)

NO

Consider more serious pathology. (Class III)

NO

Transfer to pediatric ICU (Class II)

*Note: Should a repeat event occur during the evaluation, return to top of algorithm.

Please see the back page for Class of Evidence definitions.
who had repeated cyanotic episodes in the ED was treated for pertussis. One patient with anemia was transfused. This patient had a history of prematurity and anemia and had been transfused previously on several occasions. One patient with hypoglycemia was treated with intravenous glucose. This patient had a history of prematurity and presented with an acute gastroenteritis. Blood cultures and cerebrospinal fluid studies were obtained in 62% and 38% of patients, respectively. None of these studies contributed significantly to management. A small number of patients went on to require important medical interventions despite a negative ED evaluation [supplemental oxygen (4.7%), intubation (0.7%)].

Prospective data also exist. Over a one-year period, 65 infants were evaluated after an ALTE with a standardized investigation protocol. The diagnostic evaluation included blood count, serum chemistries, lactate, ammonia, blood amino acids, urinalysis (and culture if positive), urine organic acids, urine for reducing substances, urine toxicology screen, pertussis and RSV studies, chest x-ray and EKG. Using this protocol, 13% of patients were found to be anemic. The only chemistries/metabolic assays that were significant were bicarbonate and lactate. Eleven patients had bicarbonate less than 20 mm/L and seven of these patients were diagnosed with sepsis or seizures. A “serious diagnosis” was noted in five of the seven patients with elevated lactate levels (>3mmol/L). Chest x-rays were significantly abnormal in 17 patients, 9 of which had a negative history and physical examination. One patient presented in atrial tachycardia and the EKG normalized after treatment. The other EKGs were all normal. All infants were alive at 3 years of follow-up; but, of the eight patients with recurrent ALTEs, all had significant underlying disorders. Age greater than two months was also associated with a significant disorder, relative risk 2.87 (95% confidence intervals 1.3-6.8).

A recent study also evaluated the yield of diagnostic testing in infants who had an ALTE. Data was gathered from a larger prospective study and considered all testing, both in the ED and during hospitalization. Patients were categorized based upon the contributions of the history and physical examination and diagnostic testing in the establishment of a diagnosis. In patients with positive findings in the history and physical examination (171 patients, 70.4%), 7.1% of diagnostic tests were considered contributory. The most frequently contributory tests were pertussis antigen, positive in 2 of 3 cases (67%), pH probe, 13 of 21 cases (61.9%), and upper gastrointestinal series (47.5%). In the group with a negative history and physical exam (72 patients, 29.6%), 38 of 1164 (3.3%) of tests were contributory. Again pH probe and upper gastrointestinal series were the most likely to be positive, 35.7 and 64.3% respectively. However, in this group, a patient with upper GI bleed was the only one with an abnormal blood test. All remaining blood assays (counts, chemistries, gases, metabolic screens, coagulation profile) were non-contributory as were CSF studies. Urine culture was positive in 3 of 37 patients (8.1%) and one patient (2.2%) had a positive head CT whose findings were ascribed to birth trauma.

Another important consideration is related to the issue of metabolic defects. In cases where there is a thorough history, physical exam finding, or a suspicion of a metabolic defect, care should be taken to save additional blood aliquots and arrange for their storage. Many metabolic markers are present only at the time of the event and will be missed if samples are drawn at a later time. Urgent sub-specialty consultation (genetics, metabolism, endocrine) may facilitate this process.

The most appropriate ED diagnostic evaluation of patients after an ALTE remains unclear. A focused workup based upon the findings from the history and physical examination seems most appropriate. A simplified algorithm is provided on page 10.

**Disposition**

If the impression is that an ALTE has truly occurred, there is, as yet, no data to identify a group of patients that can be safely discharged from the ED. In many instances a period of hospitalization will help to alleviate some of the family’s anxiety. If an etiology is unclear after the ED evaluation, a period of observation and monitoring may help determine the need and direction for further diagnostic testing.

Similarly, there is no data regarding the disposition of patients presenting to the ED after an ALTE who are already on home monitors. While one may consider the discharge of such patients safe medical practice, there is no evidence to support this notion. A careful history and physical examination are again important. In some cases, the events can be downloaded from the monitor but this data may not be readily accessible. An alarm does not necessarily cor-
respond to an apneic and/or bradycardic event. The parents may report a history of alarms but found the infant in no distress. Shallow breathing is often the etiology for a false alarm. In these cases, a discussion with those who initiated the monitoring may help in the selection of the most appropriate disposition. If a clinically significant event occurred, observation may be the most appropriate course.

SIDS, Apnea, and Monitoring
A natural concern for both parents and healthcare workers after an ALTE is the risk for SIDS. The literature and lay press have provided much conflicting evidence in this area. A closer look at the evidence regarding this notion is beneficial and quite revealing.

While SIDS is the focus of much attention, the cause has remained elusive. In the late 1960s and early 70s, many theories were put forth to explain this disturbing phenomenon. In fact, little agreement existed regarding even the methodology by which theories related to the cause of SIDS were tested. This changed in 1972 with the publication of the first paper with evidence supporting its hypothesis as to the cause of SIDS.72 To this day, this paper continues to have a profound influence on the evaluation and treatment of ALTEs and apnea.

From observation, it was believed that most SIDS occurrences happened during periods of sleep. Significant hemodynamic changes associated with sleep had been well-described, as was the finding that both adults and children were noted to have periods of apnea while asleep. In a landmark paper, Steinschneider presented a case series of 5 infants with apnea, two of which would eventually die from SIDS.72 These 5 infants, ages 5-40 days at first presentation were from 3 different families. Three patients came to medical attention for repeated cyanotic and apneic episodes. Two were younger siblings of the other patients. Repeated measurements of apnea, defined as no respiratory effort for two seconds after expiration, were made in an effort to quantify the amount of apnea that occurred during sleep. A quantification of the amount of apnea during sleep (referred to as the [A/D%]) for a particular infant was obtained by dividing the sum of the duration of all the apneic episodes during sleep (A) by the total sleep duration (D). Prolonged apneic episodes were defined as greater than 15 seconds as it was believed that this amount of time would not preclude successful intervention. The effect of REM vs non-REM sleep on apnea was also measured.

The five infants studied all demonstrated increased A/D% during various periods of study. The A/D% was also increased during periods of REM sleep. Many of these periods of apnea were self-limited, however some prolonged episodes were associated with cyanosis and required resuscitative efforts. Of the 5 infants studied, 2 reportedly died of SIDS.

From this paper, three inferences emerged that continue to affect the management of patients after an ALTE. (1) SIDS was believed to be strongly associated with apnea, and by inference, apneic episodes could result in SIDS. (2) SIDS could run in families, as the two infants in the study that died were siblings. (3) Patients at high risk for SIDS could be identified and home monitoring had the potential to prevent SIDS.

Other investigators were able to establish an association with apnea and SIDS. In a large study of over 1100 infants in a home monitoring program after an unexplained episode of apnea, Oren et al were able to identify infants who were at high risk for SIDS.73 During the 11 years of data collection, 76 infants had an apneic episode that was unresponsive to repeated vigorous stimulation and resolved only with mouth to mouth resuscitation. Among this group of infants with severe apneic episodes, the mortality was found to be approximately 13%. Those with repeat severe events or those who were siblings of SIDS victims had a mortality of 30% and 25% respectively.73 This same group of investigators discovered that siblings born to families who had two or more infants who had died from SIDS or monitored for apnea in infancy were also at increased risk for severe apneic episodes and SIDS.74 While there was some disagreement over the exact risk and incidence of SIDS in these patients, other work supported the initial hypotheses regarding the link between apnea and SIDS and the risk to siblings.75, 76

With the growing body of evidence to support the link between apnea and SIDS, the use of monitors flourished. Public support and demand for such monitoring devices was also a significant driving force behind the movement for home monitoring.77 In 1978, the American Academy of Pediatrics appointed a task force to study prolonged infant apnea.78 The net result was a document that acknowledged the link between SIDS and apnea. Continuous monitoring of these infants was considered an essential component of their management, both in the

1. “She looked well after the event. It seemed that no serious illness was present and she was discharged.”

Many infants appear well after an ALTE. A normal exam, however, does not exclude significant pathology. A period of observation and usually admission is often appropriate.

2. “He did have a cough, but it appeared as if it was a URI.”

Pertussis infection and RSV may present with few symptoms. Young infants will probably not have the classic “whoop” with pertussis. RSV can present as bronchiolitis or with minimal upper airway symptoms. Testing for both of these pathogens (when seasonally appropriate) is indicated.

3. “She was persistently tachypneic, but otherwise her respiratory exam was normal, as was her cardiac exam, chest x-ray and EKG. At that point, we stopped the diagnostic evaluation.”

Tachypnea may also be a sign of acidosis, suggesting a metabolic etiology. Many markers of a metabolic disorder are present only at the time of the event. When possible, blood samples obtained as soon as possible after the event should be set aside and preserved/frozen as these will be of greatest value in attempting to identify a metabolic disorder.

4. “The problem seemed to be reflux, so I sent her home.”

In many cases, an ALTE is ascribed to gastroesophageal reflux. A causative relation ship between these two processes has never been established. Many infants have reflux, and the presence of this common condition does not exclude more significant pathology.

5. “I’ve seen this patient before for the same type of event so I sent her home.”

If the impression is again that the patient had an ALTE, admission is indicated. Some data suggest that infants with repeated events are more likely to have a serious pathology.

6. “She had a small bruise on her forehead but the mother reported that she rolled up against the side of her crib yesterday. The injury was minor and I was not concerned that was non-accidental trauma. A serious head injury did not seem possible.”

Minor injuries do happen and are often accidental. When gathering history about such injuries, it is important to decide if the mechanism is consistent with the injury. This includes a consideration of age-appropriate developmental milestones. Signs of serious intracranial injury may be very subtle and if there is any physical finding suggesting injury, imaging is warranted.

7. “I decided to admit the patient. I told the family that the baby should not be discharged without a home monitor.”

Home monitoring has not been shown to prevent SIDS. Monitoring is now recommended only for a select group of patients. Discussions with the family regarding monitoring are best left to those who will provide follow-up.
inpatient and outpatient settings.\textsuperscript{78} The document did note that, despite continuous surveillance, a successful outcome for every baby could not be guaranteed.

Despite the evidence that linked apnea and SIDS, there were other theories regarding the etiology of SIDS. Among these theories was that of infanticide. This was an old theory dating back centuries whereby unexplained deaths were blamed on many causes including witchcraft and infanticide.\textsuperscript{79} Prior to the description of SIDS, parents of victims of SIDS were often accused of killing their children. The recognition of SIDS as a clinical entity prevented many parents from being falsely accused. In 1968, infanticide was noted as a possible component of post partum depression.\textsuperscript{80} A subsequent report was the first to describe child abuse by suffocation masquerading as “near-miss” SIDS.\textsuperscript{81} It described two cases where the infants had apneic episodes, were admitted to the hospital and the mother was noted to have tried to suffocate the baby during hospitalization.

While there was significant support for the apnea theory of SIDS, there was also some conflicting literature. This was particularly true with respect to the issue of risk in siblings. Kelly at al showed a higher rate of periodic breathing in siblings of SIDS.\textsuperscript{82} In a prospective study, Wilson et al found no significant difference in the number of apneic pauses, or in heart and respiratory rates in 16 patients that would eventually die from SIDS as compared to 324 controls.\textsuperscript{83} The findings from a similar study between siblings of SIDS victims or controls\textsuperscript{84} mirrored these results. The apnea theory had many who doubted its validity.\textsuperscript{77}

Many of the flaws in the apnea theory can be traced back to the initial paper that first supported this hypothesis.\textsuperscript{72} The article was a case series rather than a true study. The respiratory patterns of these infants was thoroughly described but not compared to any control patients. Apnea was noted to have occurred if there was no respiratory activity within two seconds of expiration. Most would consider such pauses physiologic in newborns and young infants. The A/D% was not a validated measurement, and values from normal patients were not reported. This methodology may have been acceptable in a case series, but it did not provide sound evidence to support a hypothesis.

Even more notable is the patients themselves. “Patient 1” was enrolled in the monitoring program after a cyanotic episode at home at 8 days of age. This patient’s family history was significant for SIDS in three siblings. The descriptions of the sibling’s deaths is as follows: “sibling 1 . . . recurrent cyanotic episodes while asleep died suddenly at 102 days of life,” “sibling 2 . . . at 48 days of age and during a bottle feeding suddenly ‘seemed to choke’ , turned blue and died” and “sibling 3 . . . following breakfast, called out and died suddenly; he was 28 months old at the time.” The history of “sibling 1” is consistent with SIDS. The death of “sibling 2” is certainly not a classic description, but the laryngeal chemoreflex has been associated with significant apneic episodes. More troubling is the description of the death of “sibling 3”. This child was well beyond the age whereby death is ascribed SIDS. The scenario of “calling out” and then dying suddenly is upsetting. Two of the patients spent significant portions of their lives in the hospital for recurrent apneic events. Both would also die at home despite the monitoring program. The net result is five siblings whose deaths were all attributed to SIDS. While there was some expectation of increased risk of SIDS in siblings of SIDS victims, this certainly went beyond those expectations. Years later, the mother of these five children would confess to their murders.\textsuperscript{77}

More recent work has failed to support apneic episodes as precursors to SIDS. The National Institute of Child Health and Human Development’s SIDS Cooperative Epidemiologic Study was a case-control study of 757 presumed SIDS cases and 1514 controls.\textsuperscript{85} No association between apnea and SIDS could be demonstrated. The Collaborative Home Infant Monitoring Evaluation was a large study that monitored over 1000 patients with ALTEs, siblings of infants who died of SIDS, preterm infants and healthy term infants.\textsuperscript{86} Apnea and bradycardia alarms were noted in all groups of infants. Preterm infants less than 43 weeks postconceptual age were the only subgroup that was found to be at risk for extreme events. In this study, extreme apnea was defined as episodes lasting longer than 30 seconds and extreme bradycardia was defined as more than 10 seconds of a heart rate of less than 60 beats per minutes (bpm) in infants less than 44 weeks postmenstrual age and less than 50 bpm in infants greater than 44 weeks postmenstrual age. The investigators also reported that the high frequency of obstructed breathing in study participants would likely be undetected by most home monitors.

The 2003 Policy Statement on Apnea, Sudden...
Infant Death and Home Monitoring from the American Academy of Pediatrics reflects the growing evidence against the apnea theory.\(^7\) It recommends that home monitoring not be used to prevent SIDS. It suggests home monitoring may be appropriate for premature infants at risk for recurrent episodes until approximately 43 weeks postmenstrual age or until after the cessation of the extreme episodes, whichever comes last. It also states that parents should be advised that home monitoring has not been proven to prevent SIDS.

### Outcomes

In many cases, the outcome of infants after an ALTE is related to the underlying etiology. A number of short-term studies have considered neurodevelopmental issues in children with a history of ALTE. Early data suggested that infants less than 3 months of age were likely to have abnormalities of muscle tone, in particular hypotonia.\(^8\) This seemed to improve with age but by age two, approximately 40% of patients still exhibited neurological and developmental abnormalities. Impairments of gross motor development were noted in patients after an ALTE as compared to healthy siblings.\(^8\) This difference was not noted when these patients were compared to their age-matched playmates.\(^8\) Toddlers with a history of ALTE are more likely to have loud snoring, breath-holding spells, resistance to bedtime, and some mild aggressive behavior.\(^8\)

Less data exists regarding long-term outcomes. The study with the longest follow-up considered children in 11-15 years of age.\(^9\) This small, single-center study identified 21 cases of ALTE between 1985 and 1990 that were admitted for overnight polygraphic recordings after an ALTE. A follow-up study was started in 2000. From the group of 21 patients, 7 could not be traced. A group of 12 controls was selected from a group of normal patients whose parents had come to the center due to increased media attention of SIDS. Neurologic, gross and fine motor and behavioral evaluations were made for all subjects. One patient with a history of ALTE had motor and severe learning disabilities and aggressive behavior disorder. He also had epilepsy. Patients with a history of ALTE were more likely to have minor neurologic defects as compared to controls. Examples of these defects included less than optimal performance of heel-toe-gait, walking on tip-toes, walking on heels, and standing or hopping on one leg. Gross and fine motor abilities as well as behavior were noted to be the same in both groups.

Another study showed that cognitive performance was independent of ALTE history in a group of patients between ages 6-10 years.\(^9\)

### Summary

Infants presenting after an ALTE continue to be a clinical challenge. The history can be difficult to obtain and the physical examination findings may be subtle or absent. The differential diagnosis is very broad and etiologies can range from clinically unimportant to life-threatening. A thorough history and careful physical examination are of utmost importance. Diagnostic testing should stem from historical information and clinical findings. Although many patients will have a benign clinical course, a period of observation is almost always warranted.

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Physician CME Questions

1) The acronym ALTE most appropriately stands for:
   a. Acute Life-Threatening Event
   b. Acute Pediatric Life-Threatening Events.
   c. Apparent Life-Threatening Event
   d. All of the above

2) Which of the following must be present for an event to be considered an ALTE?
   a. Cyanosis
   b. Change in tone
   c. Gagging
   d. None of the above

3) The incidence of which of the following is decreasing?
   a. ALTE
   b. SIDS
   c. Both (a) and (b)
   d. None of the above

4) Which of the following risk factors for SIDS has been shown to be a risk factor for ALTE?
   a. Prone sleeping
   b. Pacifier use
   c. Multiple gestation
   d. None of the above

5) Gastroesophageal reflux:
   a. Is rare in infants
   b. Is worse during supine sleeping position
   c. Worsens progressively during the first year of life
   d. Has been shown to always precede an apneic episode

6) Respiratory syncitial virus (RSV) infection:
   a. Will not cause apnea without symptoms of bronchiolitis
   b. Causes concern for apnea, particularly in infants 3-6 months of age
   c. May be indistinguishable from other respiratory infections in young infants
   d. None of the above

7) Patients with ALTE:
   a. typically have less diaphragm strength than control patients
   b. are more likely to have family members with sleep-disordered breathing
   c. usually have a bacterial etiology
   d. none of the above

8) From the list below, the most common bacterial etiology of an ALTE is:
   a. Urinary tract infection
   b. Bacteremia
   c. Meningitis
   d. Tonsillitis

9) Ondine’s Curse is:
   a. a common cause of ALTE
   b. a neuromuscular disorder
   c. an autonomic disorder
   d. none of the above

10) Risk factors for an underlying metabolic disorder as an etiology for ALTE include all of the following except:
    a. Splenomegaly
    b. Hepatomegaly
    c. Family history of SIDS
    d. Recurrent events/episodes

11) Significant head trauma as a cause for ALTE:
    a. is never subtle in presentation
    b. can usually be excluded based on the physical examination
    c. should prompt the physician to attempt to identify a perpetrator
    d. all of the above

12) Concerns for intentional suffocation include all of the following except:
    a. ALTE with different care providers
    b. Death of infant at greater than 6 months
    c. Death of 1 or more siblings
    d. Simultaneous or near-simultaneous death of twins

13) Hemoglobin levels in patients with ALTE:
    a. tend to be lower in patients with ALTE
    b. are most often so low as to require transfusion
    c. both (a) and (b)
    d. none of the above
14) Evidence supports which of the following diagnostic tests for every patient with an ALTE?
   a. glucose
   b. blood count
   c. ammonia
   d. none of the above

15) Which of the following tests is likely to be helpful in establishing a diagnosis in a patient with an ALTE that has a non-contributory history and physical examination?
   a. CSF studies
   b. Urine organic acids
   c. Head CT
   d. None of the above

16) Home monitors:
   a. have never been proven to prevent SIDS
   b. are indicated for all patients after an ALTE
   c. provide a means to safely discharge a patient home after an ALTE
   d. have good specificity for apneic episodes

**Class Of Evidence Definitions**

Each action in the clinical pathways section of Pediatric Emergency Medicine Practice receives a score based on the following definitions.

**Class I**
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

**Level of Evidence:**
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

**Class II**
- Safe, acceptable
- Probably useful

**Level of Evidence:**
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

**Class III**
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

**Level of Evidence:**
- Results consistently positive
- Less robust RCTs
- Control studies

**Indeterminate**
- Continuing area of research
- No recommendations until further research

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