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REVIEW ARTICLE

Infantile Apparent Life-Threatening Events, an Educational Review

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Abstract

Many physicians have received a frantic call from anxious parents stating that their child had stopped breathing, become limp, or turned blue but then had recovered quickly. An apparent life-threatening event (ALTE) is defined as "an episode that is frightening to the observer, and is characterized by some combination of apnea, color change, marked change in muscle tone, choking, gagging, or coughing". The incidence of ALTE is reported to be 0.05% to 6%. The knowledge about the most common causes and factors associated with higher risk of ALTE could be resulted in a more purposeful approach, improving the decision making process, and benefiting both children and parents. The aim of this review article was to report the epidemiology, etiology, evaluation, management, and disposition of ALTE. Infants with an ALTE might present no signs of acute illness and are commonly managed in the emergency settings that often require significant medical attention; hence, the emergency medicine personnel should be aware of the its clinical importance. There is no specific treatment for ALTE; therefore, the clinical evaluations should be focused on the detection of the underlying causes, which will define the outcomes and prognosis. ALTE is a confusing entity, representing a constellation of descriptive symptoms and signs; in other words, it is not a diagnosis. There are multiple possible etiologies and difficulties in evaluating and managing infants with these events, which are challenges to primary care physicians, emergency medicine specialists, and subspecialty pediatricians. The evaluation of these events in infants includes a detailed history, appropriate physical examination, diagnostic tests guided by obtained clues from the history and physical examination, and observation in the emergency department.

Key words: Infantile apparent life-threatening event; death, sudden; pediatrics; emergency medicine

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Introduction:

An apparent life-threatening event (ALTE) was defined as "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, gagging, or coughing" (1, 2). This definition replaced the term "near-miss sudden infant death syndrome" that implied a close association with sudden infant death syndrome (SIDS) but was subsequently dismissed based on scarce evidence of the overlap between ALTE and SIDS. Whether SIDS and ALTE are strictly correlated is still a major argument among neonatologists (3, 4). Although a number of ALTE risk factors are similar to those of SIDS, the differences warrant a separate focus on ALTE beyond that on SIDS (5). ALTEs presenting to the emergency department (ED) might remain as a single, unexplained event or be attributable to numerous causes, ranging from minor to serious ones (6). Knowledge about the most common causes and factors associated with higher risk of ALTE could result in a more purposeful approach, improving the decision-making process, and benefiting both the infants and their parents (6). Infants with ALTE usually present with an acute and unexpected change in behavior that has alarmed the caregivers (5). They might present with signs of acute illness that usually mandates management in the emergency medicine settings. These patients often require significant medical attention as well as intervention; hence, the emergency medical service (EMS) personnel should be aware of the clinical importance of these events to provide timely and thorough medical evaluation and treatment for infants meeting the criteria for an ALTE (7). Demographic data of cases with ALTE are obtained from children admitted to hospitals or EDs and because not all the children are brought for evaluation, the precise incidence of ALTE is not clear. The reported incidence ranges from 0.05% to 6% or is

estimated at 2.4 in every 1000 live births (5, 8, 9). The incidence of ALTE among neonates is reported to range from 1.57 to 2.46 in every 1000 live births (4, 10). Most of the ALTEs occur in children younger than one year old (11, 12). In most published studies, a substantial portion of reported patients with ALTE were in neonate or at least younger than three months old with 50% to 80% being younger than two to three months old (9, 13-15). The median age was two months and 50% of infants showed normal findings on clinical examinations (16, 17). It has been reported that 2.27% of hospitalized children are the Infants with ALTE (18). Based on above-mentioned, the aim of this review was to present the epidemiology, etiology, evaluation, management, and disposition of ALTE.

Etiology

The underlying etiology of ALTE varies and an episode of ALTE should be considered the manifestation of other conditions rather than a diagnosis. An etiology would be found in one-half of patients, implying a potential for an intervention that could eliminate further events. The most frequent problems associated with ALTE are gastrointestinal (50%), neurologic (30%), respiratory (20%), cardiovascular (5%), metabolic and endocrine (< 5%), or other problems such as child abuse. Despite through evaluations, no specific diagnosis would be made for the remaining patients, i.e. idiopathic cases (2, 19). The approach to investigate and manage an ALTE during admission is unstructured. A large number of patients are discharged from the ED and inpatient service with different diagnoses, mostly with convulsion, febrile convulsion, gastroesophageal reflux disease (GERD), and lower respiratory tract infection. The diagnosis changes in those attending more than once for ALTE (16). ALTE might occur in the first 24 hours of birth, particularly within the first two hours. Events are often related to a potentially asphyxiating position.

Parents might be too fatigued or unable to assess their infant's condition correctly (20). Of the infants with ALTE, 83.3% appeared to be in no distress, 13.3% mild, and 3.3% moderate distress. In most patients, findings of the general appearance and vital signs were not clinically abnormal (7).

Differential Diagnosis

The ALTE might be associated with a variety of underlying diseases (21). Epidemiologic studies found that the most frequent causes of ALTE were consecutively GERD, respiratory infections, and seizures (22, 23). Table1 lists the common, uncommon, and rare diagnoses assigned to patients with ALTE. Common causes are discussed independently (19, 21-23)(table 1).

Gastroesophageal reflux disease

GERD was the most common diagnosis among patients with ALTE (24). GERD induces significant histopathologic changes in larynx mucosa (25). Given the temporal correlation between peak age of ALTE and that of GERD, and the fact that reflux of gastric contents into the hypopharynx can trigger laryngospasm, a diagnosis of GERD provides an easy explanation for an ALTE. However, researchers have been unable to demonstrate a temporal association between episodes of GERD on pH probe and ALTEs or apneic events (26, 27).

Respiratory Disorders

Respiratory disorders are another common diagnosis in patients with ALTE; however, the frequency of diagnosis is widely varied (28). This might be due to epidemic bronchiolitis, pertussis, or lower respiratory tract infections (29). Up to 20% of infants younger than six months old, who were hospitalized due to infection with respiratory syncytial virus (RSV) had apnea and this association was strongest during the first month of life and in preterm neonates (30). Apnea occurred in 0.5% to 12.0% of children younger than two years of age with pertussis (31, 32). In infants with ALTE, prolonged respiratory events are associated with ineffective esophageal motilities, characterized by frequent primary peristalsis and significant propagation failure, which is suggestive of dysfunctional regulation of swallow-respiratory junction interactions. Hence, treatment should target the proximal aerodigestive tract rather than GERD (33).

Seizures

Seizures are diagnosed in 4% to 7% of infants with ALTE (34). ALTE might be the first sign of an epileptic seizure. Diagnosis is often difficult because the interictal electroencephalogram (EEG) findings are usually normal or show nonspecific changes; moreover, GERD

Table 1: Reported final diagnoses for patients with apparent life-threatening events

Common	Less Common	Rare Reported
Gastroesophageal reflux disease	Pertussis	Arrhythmia or other cardiovascular
Seizure/febrile seizure	Inflicted injury	diseases
Upper/lower respiratory tract infection	Poisoning	Anemia
Misinterpretation of benign process such	Serious bacterial infection	Breath-holding spell
as periodic breathing	Electrolyte abnormality	Metabolic diseases
Vomiting/choking episode		Anatomic maxillofacial obstruction

might mimic these events (35). During the etiologic investigation of ALTE, first seizures and epilepsy should be included in the differential diagnosis and ictal recordings would be important tools to confirm these diagnoses (36-38). Seizures are secondary to underlying causes such as congenital brain malformation, metabolic disorders, electrolyte abnormalities, prenatally acquired brain injury, or intracranial bleeding (including nonaccidental head trauma); therefore, these possibilities must be considered during assessments (39).

Trauma

The diagnosis of child abuse should be considered in patients with ALTE. The evaluation of ALTEs should include funduscopic examination as ALTEs and retinal hemorrhages are associated with child abuse. Retinal hemorrhage was detected in 1.4% of infants with ALTEs (40). The diagnosis of inflicted traumatic head injury cannot rely on the finding of retinal hemorrhage alone, but the finding of severe bilateral retinal hemorrhage particularly with retinal folds or detachments is suggestive of the diagnosis (41). Child abuse was detected in 2.3% of patients with ALTE (40). Infant with inflicted head injury might appear well on presentation with no external signs of abuse (42, 43); hence, inflicted head injury must be considered in a patient who has an ALTE unless an alternative cause is readily apparent (14).

Poisoning

A large number of children referred to the ED with ALTE had positive toxicology screening results. In particular, a number of these children were found to be given an over-the-counter cold medicine. The most frequently detected medications were acetaminophen, amphetamine, benzodiazepines, cocaine, codeine, meperidine, methadone, phenobarbital, and phenothiazine (44, 45). Thus, toxicological screening tests should be included in routine evaluation of children with ALTE (44) and poisoning by a caregiver (Munchhausen by proxy) should be added to the differential diagnosis of these infants. Moreover, urine drug screening tests should be considered in the evaluation (45). Induced illness is a severe form of abuse that might cause death or permanent neurologic impairment. It might be accompanied by other severe abuse forms, which results in behavioral disorders. Detection of this abuse requires a closed and focused collaboration of hospitals and community's child health professionals, child psychiatrists, social workers, and police officers (46).

Bacterial Infection

Serious bacterial infections (SBIs) must be considered in all febrile infants with ALTE. The reported rates range from 0% to 8.2% and the possibility of bacteremia, meningitis, or urinary tract infection should be considered in infant presenting with an afebrile ALTE. The concern is greatest for infants younger than 60 days of age who might show few other symptoms to indicate the possibility of SBIs (47). In patients with ALTE who appear well without suggestive signs of SBI, it might be possible to forego routine sepsis evaluation beyond a chest radiograph and urine culture without risking a serious missed diagnosis (42). Routinely, children who present to the ED with ALTE do not need to undergo a full evaluation of SBI, while infants with such situation require infectious evaluation for SBI (48, 49).

Breath holding spells

Breath holding spells (BHS) are among the common benign paroxysmal nonepileptic disorders occurring in otherwise healthy children (50). The pathogenesis of BHS is not understood well, but some studies suggested that imbalance between the sympathetic and parasympathetic activity could play role in developing such a manifestation (51). The reported prevalence ranges from 0.1% to 4.6% in the general population (52). The diagnosis is usually made through description or observation of typical attacks characterized by a sequence of clinical events, beginning with a provoking event such as minor trauma or emotional upset, followed by a noiseless state of expiration accompanied by skin color change (paleness or cyanosis), and finally, loss of consciousness and postural tone (51). Based on the skin color change during the attacks, BHS has two types: pallid and cyanotic; however, some children might experience mixed-type attacks (53). Overall, the cyanotic type is more common and the ratio of cyanotic to pallid type is 3:1. Although these attacks were previously considered as benign and self-limited in children between six and eight years of age, recent studies have shown that many of these patients would develop syncope attacks in the future (54). Rarely, these spells might be an initial symptom of long QT syndromes or paroxysmal cardiac rhythm abnormalities (53). Therefore obtaining an electrocardiogram to evaluate prolonged QT syndrome is strongly recommended. Although BHS should be a diagnosis of exclusion in younger patients, some ALTEs might present by early manifestations of BHS (54).

Management

Specific information that should be obtained in the history and physical examination is outlined in Table 2 (54, 55).

Table 3 reviews the medications type and doses that might be required for the treatment of these patients, depending on their clinical picture (55-57).

Patients with ALTE can be easily categorized into one of the following three groups. The first group consists of those with clear diagnosis of ALTE obtained from the history or physical examinations. The second group included the infants without immediately clear diagnosis but appearing unstable. The third group, which is the largest, consists of well-appearing

Table 2: Important information of patient with apparent life-threatening event

Past Medical History	Prematurity (birth before 37 weeks)
	Prior hospitalization, surgery, or ED visits
	History of apnea
	Prior respiratory difficulties (snoring or stridor)
	Prior feeding difficulties (choking, gagging, or coughing with feeds)
	Immunization status (pertussis)
	history of urinary tract infection
Family History	History of SIDS or sudden death
	Cardiac arrhythmias or congenital heart disease
	Seizure disorder
	Metabolic diseases
Event History	Duration of event (< 1 min, 1-5 min, or > 5 min)
	Required Resuscitation (e.g., stimulation, mouth-to-mouth breath, chest compressions)
	Temporal relationship of feeding, sleeping, crying, vomiting, choking, or gagging
	Skin color (cyanosis, pallor, or flushing)
	Change in tone (including seizure activity, flaccid, or spastic)
	Central vs. obstructive pattern of apnea (i.e., apparent respiratory effort)
	Number of ALTEs experienced within 24 h of presentation
	Episodic vs. sustained change in mental status (syncope, postictal phase, irritability, or obtundation)
	Correlation with feeding (at feeding time, few minute after feeding, or not related feeding)
	Seasonal distribution (spring, summer, autumn, or winter)
	Asleep or awake (awake, asleep, or both)
	Position of the neonate (supine or prone)
	Place of attack occurrence (parent's lap or cradle)
Review of Systems	Respiratory symptoms or other intercurrent illness
	Period of fasting (e.g. recent onset of sleeping through night)
	Medication use, medications in the home or used by breastfeeding parent
	Possible trauma
Social History	Possibility of follow-up
	Comfort level of parents
	Parental concern for abuse
	Parental psychiatric issues or marital stress (e.g. absentee parent)
	exposure to the infectious agents (pertussis, RSV, upper respiratory infection, lower respiratory tract infection)

ALTE, apparent life-threatening event; ED, emergency department; SIDS, sudden infant death syndrome; and RSV, respiratory syncytial virus.

infants with a concerning history, but their physical examinations show normal or noncontributory results.

Patients with a Clear Diagnosis

ALTEs are heterogeneous disorders that might frighten infants' caregivers (57). ALTEs are not a diagnosis and therefore, the attention must be turn to find the underlying diseases (2). With a careful history review, physical examination, and some basic laboratory investigations, the main causes of ALTE might be discovered. Invasive investigations like lumbar puncture (LP) should be reserved for ill patients or for those with laboratory or clinical impressions suggestive of central nervous system infections. Clinicians should alarm the parents about recurrence of these episodes and train them on the primary life support activities as well as on avoiding any harmful reactions (58). After an ALTE work-up, hospitalization would be required if the etiology was life-threatening (57).

Unstable patients without a clear diagnosis

For unstable patients without a clear diagnosis, the priority is stabilization, which requires assisted ventilation for infants with persistent compromised ventilation or those with frequent apnea requiring monitoring and stimulation in the ED. In such a situation, head injury, sepsis, metabolic or electrolyte disorder, poisoning, complicated

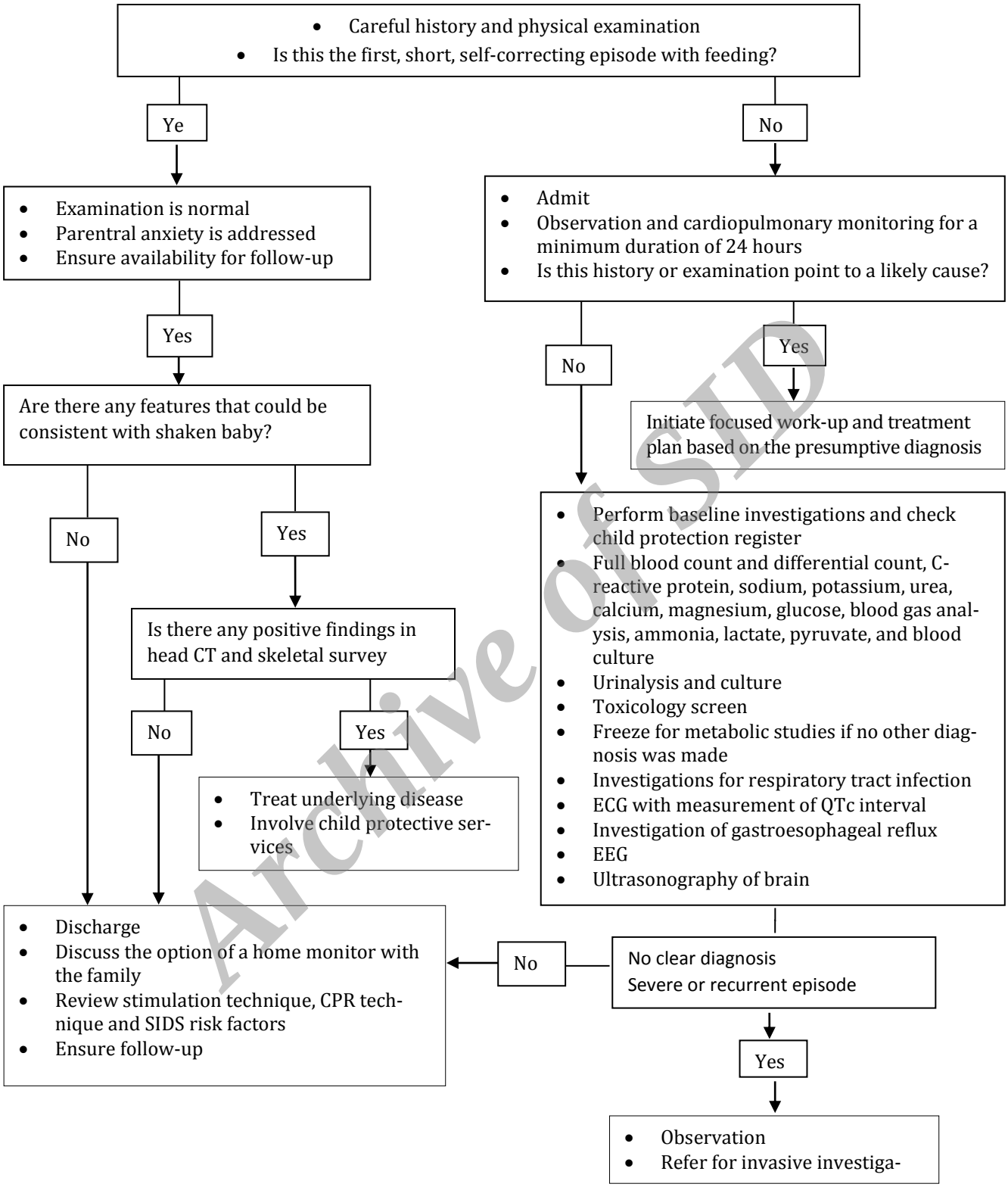

Figure 1: Investigation plan for an apparent life-threatening event

Table 3: Common intervention for ill patient with apparent life-threatening event

Indication	Medication/Intervention	Dose/Size
Hypoglycemia	Glucose	5-10 mL/kg of 10% dextrose in water, IV
Hyponatremia	3% Normal Saline	3-5 mL/kg bolus, IV
Hypocalcemia	Calcium	50-100 mg/kg calcium gluconate or 20 mg/kg calcium chloride, IV
Infection	Cefotaxime	50 mg/kg, IV
	Ampicillin	50 mg/kg, IV
Anemia	Packed red blood cells	10 mL/kg, IV
Hypotension	Normal Saline	20 mL/kg, IV
Metabolic disease	10% dextrose in one-fourth normal saline	1.5 maintenance (6 mL/kg/h for the first 10 kg)
Hypoventilation or frequent apnea	Endotracheal intubation	3.0 mm^3 for preterm; 3.5 mm^3 for term neonate; and 4.0 mm^3 for older infant

IV: Intravenous; kg: Kilogeram; mL: Mililiter; h: houre; mm^3: Cubic millimeter

pertussis, and bronchiolitis (in the neonate or ex-preemie) are the most likely causes (59). Infants with ALTE should be investigated for the presence of respiratory pathogens, particularly Bordetella pertussis and RSV. These infections might be accompanied by clinically undetected baseline and episodic hypoxemia (60, 61).

Stable patients without precise diagnosis

In the clinical situation, when the patients with ALTE are considered to be idiopathic, some clinicians advocate a minimal evaluation with unexpansive tests for early detection of a rare, yet potentially devastating disease (e.g. infection or metabolic disease), to prevent long-term complications (62). This evaluation would include a complete blood count, C-reactive protein, basic metabolic panel, ammonia, lactate, pyruvate, blood gas measurement, urinalysis, toxicology screen, electrocardiogram, and microbiologic assessment for B. pertussis and RSV infections (62, 63).

Laboratory and paraclinical tests

When the history includes an awake, supine infant fed in the last hour, GERD would be the most convincing diagnosis (64). In this case, a pH probe study is the best test although the nonacid reflux cannot be captured. Although temporal association might be seen between acid reflux and symptoms, this test does not establish causality (65). A chest radiograph can be obtained, as indicated by history and physical examinations. While bacterial meningitis, sepsis, and urinary tract infections account for approximately 9% of the diagnoses, they should be considered in an ill-appearing infant (39). EEG had a 15% sensitivity for diagnosing epilepsy (66). Some authors suggested that EEG should be taken from those with recurrent ALTE (63). Some studies have reported the very high rates of cardiac arrhythmia including prolonged corrected QT interval, premature ventricular or atrial beats, or sinus node irregularity in full-term and otherwise healthy infants with previous ALTEs who were undergone a 24-hour continuous holter monitoring (64). Many metabolic conditions are triggered by fasting and might be accompanied by symptoms of hypotonia, lethargy, or vomiting. In these cases, laboratory evaluation including blood glucose, pH, ammonia, lactate, and pyruvic acid levels might help to find the underlying cause (2). It seems that performing LP is not necessary for all neonates with an episode of ALTE, especially those with normal findings on their physical exams. However, recommendation of LP might be reserved cases with high index of suspicion (13). If there is a suspicion of abuse or trauma, the evaluation should include ophthalmologic exam for retinal hemorrhage, head computed tomography (CT), and skeletal survey (67).

Disposition

Multiple possible etiologies and difficulties in evaluating and managing infants with ALTE pose a challenge for primary care physicians, emergency medicine specialists, and subspecialty pediatricians. The evaluation of these infants should include a detailed history, thorough physical examinations, and appropriate diagnostic tests based on the clues obtained from the patient's history and physical examinations (62). Only 12% of infants referred to the ED with ALTE need a significant intervention warranting hospital admission (57). Regarding infants with ALTE and no acutely ill appearance, there is no consensus on the minimal diagnostic evaluations and on the part of history and risk factors that should lead a practitioner toward admission to or discharge from the ED. Clinical judgment remains a very important part of the decision-making process (68). A practical algorithm listed in Figure1 (55, 57, 68). The ALTE term is nonspecific and describes a cluster of symptoms with many possible causes. In the clinical situation when the etiology of the ALTE is not established after a detailed history and comprehensive physical examination, which might be considered as idio-

pathic, some clinicians advocate a minimal diagnostic evaluation. The three following variables could identify most but not all of the infants with ALTE and necessitate admission: the obvious need for admission, significant medical history, and more than one ALTE episode during 24 hours. These variables require external validation and reliability assessment before clinical implementation (67).

Conclusion:

Children with ALTE referred to ED with anxious parents. Several factors such as the number and type of ALTE manifestations, underlying diseases, and parents' situation would affect the patient's management. The evaluation of these infants including detailed history, appropriate physical examination, and close observation in ED. Further studies are recommended to identify the etiologic factors and appropriate management of children with ALTE.

Conflict of interest:

None.

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