

## Apparent Life-Threatening Events in Neonatal Period: Clinical Manifestations and Diagnostic Challenges in a Pediatric Referral Center

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### Abstract

**Objective:** Apparent Life-Threatening Events (ALTEs) is an episode that is frightening to the observer and is characterized by some combination of apnea, color change, altered muscle tone, choking, and gagging. This study was designed to evaluate and follow up neonates who presented with clinical manifestation of an ALTE in a year.

**Methods:** In this prospective observational study, all of the neonates with episode of ALTE who were admitted to the Children's Medical Center (CMC) in Tehran, from June 15<sup>th</sup> 2010 to May 14<sup>th</sup> 2011 were enrolled in the study. Data from patients consisting of history, physical examinations, and paraclinical findings were recorded in a checklist and all followed up 3 to 6 months after discharge.

**Findings:** During the study period 18 neonates were admitted due to ALTE episode(s) with mean age of 15±13 days. Nine (50%) neonates had previous attacks of ALTE. The most frequent complaint was cyanosis in 12 (67%) and apnea in 8 (44%) patients. In 10 (56%) the event lasted less than one minute, 13 (72%) were awake, 17 (95%) in supine position and 13 (72%) on their parent's lap. Primary antagonistic impression on admission was sepsis in 11 (61%) and concomitant seizure in 5 (28%). The most common final diagnosis according to repeated physical examinations, result of paraclinical investigations and follow up was sepsis 4 (22%) and aspiration 9 (50%). ALTE recurred in none of the neonates during follow up.

**Conclusion** The rate of ALTE seems to be higher than in this study owing to high incidence of recurrent ALTE. Although most of these attacks regress spontaneously, more attention should be paid for the underlying diseases.

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**Key Words:** Apparent Life Threatening Events; Infant; Neonate; Sepsis; Seizure

### Introduction

Apparent life-threatening events (ALTEs) according to National Institute of Health (NIH) definition in 1986, is explained as an episode in infantile period that is frightening to the observer and is characterized by some combination of

apnea, color change, altered muscle tone, choking and gagging<sup>[1]</sup>. Exact prevalence of these events are not clearly known, because most of present reports are based on admitted patients in hospital setting, and it is not unpredictable that most of these patients do not seek medical attention or specially hospital admission. However, available

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published reports about prevalence of ALTE are ranging from 0.5% to 0.6% of attendings to the medical centers<sup>[2,3]</sup> or 2.4 in 1000 live births<sup>[4]</sup>. Overall most episodes of ALTE occur in infants less than one year of age without any identified causes<sup>[2,3]</sup>. It Any relationship between ALTE and sudden infant death syndrome (SIDS) is unclear<sup>[5,6]</sup>. This study was designed to evaluate neonates a referral children hospital in Tehran with clinical manifestation of an ALTE in one year. In addition, it was arranged to follow them regarding outcome and final diagnosis in this critical age. To our knowledge this is the first report of a prospective study on ALTE in the neonatal period from this region.

## Subjects and Methods

In this prospective observational study, all of the neonates with episode of ALTE who were admitted to the Children's Medical Center in Tehran affiliated with Tehran University of Medical Sciences from June 15<sup>th</sup> 2010 to May 14<sup>th</sup> 2011 entered this study. ALTE was demonstrated as according to NIH definition as sudden onset of episode with apnea, change in color (cyanosis, pallor or flushing), obvious alteration in musculature tonicity (limpness or stiffness), choking or gagging in the infant<sup>[1]</sup>.

The CMC is the Pediatric Center of Excellence in Iran. It is not only one of the most important tertiary referral hospitals in the country accepting plenty of patients from Tehran and surrounding cities with annually around 124500 visits.

Patients in this study were considered as full term neonates from birth to 28th day of life and preterm newborns with corrected gestational age of 40 weeks and 28 days old.

Patients with severe prematurity (gestational age less than 30 weeks), corrected gestational age less than 37 weeks, known case of congenital heart disease, history of seizure and chronic lung disease were excluded from the study.

After being approved by the Ethics Committee of Faculty of Medicine of Tehran University of Medical Sciences, the aim of this study was explained to the family and a written consent was obtained from parents. All interventions on human

subjects have been performed in agreement with the ethical standards laid down in the Declaration of Helsinki of 1964.

**Data collection:** A check list was designed to record all data from patients similarly; which was assigned by review of literatures and experts' consultation. The check list included three separate sections: history, physical examination, and paraclinical investigations. Data was collected by one of the investigators as soon as possible after admission from the infant's caregiver, who observed the episode. The sources of information were the infant's mother in all. Data were collected continuously till the time of discharge and followed up further for three to six months after discharge from the hospital. Primary impression at time of admission and final diagnosis according to repeated physical examinations, review or completion of paraclinical investigations, and in some instances after follow up were also recorded.

**Follow up:** A telephone survey accomplished nearly three to six months after hospital discharge and sometimes repeated thereafter if any medication was prescribed or discontinued recently. In each conversation recurrence of the episode, development of the infant, and any other medical problem or medication usage was also asked.

Data was analyzed by SPSS software version 16 (SPSS Inc, Chicago, Illinois, USA). Mean and standard deviation were used for quantitative variables and frequency and percentage for qualitative ones.

## Findings

During one year period of the study, 1633 neonates were visited in the emergency department (ED) of CMC and 18 of them admitted due to ALTE episode(s). The overall incidence of ALTE in neonatal period in our study was 11 in 1000 (1.1%) newborns that were brought to the ED.

They were 1 to 50 days old with mean age of  $15 \pm 13$  days. Mean birth weight was  $2.9 \pm 0.6$  Kg. The characteristics of neonates with ALTE are shown in Table 1. Family history of seizure was positive in sibling of one neonate. One mother had



**Table 1:** Characteristics of neonates who presented with ALTE (n=18)

Characteristics		Frequency (%)
<b>Gender</b>	Boy	15 (83)
	Girl	3 (17)
<b>Gestational age</b>	≤37 weeks	8 (44)
	> 38 weeks	10 (56)
<b>Route of delivery</b>	Cesarean section	11 (61)
	Vaginal delivery	7 (39)
<b>Perinatal asphyxia</b>		2 (11)
<b>Birth weight</b>	Less than 2500 gr	7 (39)
	2501-4000 gr	11 (61)
<b>Second hand smoker</b>		5 (28)
<b>Rank in family</b>	First child	7 (39)
	Second child	10 (56)
	Third child	1 (5)
<b>Feeding</b>	Exclusive Breast milk	14 (78)
	Formula plus breast milk	4 (22)
<b>Parent's consanguinity</b>		3 (17)
<b>Recent usage of prescribed or OTC drug</b>		10 (56)

OTC: Over the counter; ALTE: Apparent life-threatening events

history of hypothyroidism, whose neonate had also abnormal thyroid function test compatible with transient hypothyroidism. Nine (50%) neonates had previous attacks of ALTE before the

last episode, while 6 (33%) had multiple attacks in one day.

The clinical presentation of ALTE episodes among these neonates is demonstrated in Table 2.

**Table 2:** Clinical presentation of neonates who presented with ALTE (n=18)

Clinical presentation		Frequency(%)
<b>Apnea</b>		8 (44)
<b>Change in color</b>	Cyanosis	12 (67)
	Flushing	5 (28)
	Pallor	1 (5)
<b>Tonicity</b>	Normal	10 (56)
	Flaccid	6 (33)
	Spastic	2 (11)
<b>Choking</b>		7 (39)
<b>Gagging</b>		7 (39)
<b>Correlation with feeding</b>	At feeding time	3 (17)
	A few minutes after feeding	7 (39)
	Not related to feeding	8 (44)
<b>Seasonal distribution</b>	Spring	4 (22)
	Summer	5 (28)
	Autumn	2 (11)
	Winter	7 (39)
<b>Duration</b>	Less than 1 minute	10 (56)
	Between 1 to 5 minutes	5 (28)
	More than 5 minutes	3 (17)
<b>Time of episode</b>	Frequently occurred	8 (44)
	11 am to 6 pm	5 (28)
	7 pm to 1 am	5 (28)
<b>Asleep or awake</b>	Awake	13 (72)
	Asleep	4 (22)
	Both situations	1 (5)
<b>Position of the Neonate</b>	Supine	17 (95)
	Prone	1 (5)
<b>Place of attack occurrence</b>	Parent's lap	13 (72)
	Cradle	5 (28)

ALTE: Apparent life-threatening events

In 5 (28%) neonates, attacks subsided spontaneously, in 10 (56%) neonates caregivers provided gentle stimulation to the neonate like bellowing to infant's face, but 3 (17%) had experienced more severe stimulation i.e. upside down position or chest compression by an untrained caregiver. Only one neonate was brought to the hospital by an emergency service, the others were carried to the hospital by parents.

Gastroesophageal reflux disorder (GERD) was determined by presentation of some symptoms or complaints asked from caregivers; however one (5%) had history of occasional regurgitation and another, irritability after feeding. Other complaints like loss of appetite was reported in three (17%) neonates, inappropriate weight loss in one, symptoms of upper respiratory tract infection like coryza and cough were reported in four (22%). Six (33%) had history of close contact with one who had suffered from an acute respiratory illness. Although fever was mentioned by parents of two neonates, but only one was febrile on arrival.

Physical examination of infants at time of admission revealed 13 (72%) in good condition, and 5 (28%) seemed ill, tachypnea in 2, and low

pulse oximetry in one. A neurologic exam was done in all of them on arrival and repeated one day later. Only in one 50 day old 32 weeks preterm newborn infant some degree of persistent hypotonia was found.

Laboratory workups were performed on clinical judgment; frequency and results are shown in Table 3. Seventeen (95%) were admitted in the neonatal intensive care unit (NICU) for complete monitoring and further investigation. Only one was monitored in ED and transferred to the level 2 neonatal ward after 24 hours. The mean duration of hospitalization was  $9 \pm 3$  (3 to 14) days.

Seventeen of 18 have been followed up. Mean duration of follow up was  $4.9 \pm 1.5$  months. Three patients (17%) were followed for 3 months, 11 neonates (61%) between 4 to 6 months and remaining 3 (17%) more than 6 months. Follow ups were done by phone call that happened once in 14 (78%); two times in 2 cases (11%), and three times in one case.

Primary antagonistic impression on admission was sepsis in 11 (61%) neonates, sepsis with concomitant seizure in 5 (28%), and aspiration pneumonia in 2 (11%). Four out of 5 neonates

**Table 3:** Laboratory investigations and abnormal findings in neonates who presented with ALTE (n=18)

Laboratory and paraclinical investigation	Frequency (%)	Notes
Complete Blood Cell count	18 (100)	High WBC count in 2, anemia in 1 neonate.
Arterial blood gas	18 (100)	In some cases $\text{HCO}_3^-$ was less than 20 meq/l but in repeated test few hours later it showed normal values.
Electrolyte and biochemistry assessment <sup>‡</sup>	18 (100)	Hypocalcemia in 2, one of them had vitamin D deficiency and hypomagnesaemi, the other one had normal level in repeated evaluation.
Blood culture	18 (100)	All had negative culture.
Urine analysis and culture	18 (100)	All had normal urinalysis and negative culture
Chest X-Ray	18 (100)	Was normal in 13 (72 %) cases, with evidence of aspiration, pneumonia in 4 and sign of viral pneumonia in one
C-reactive protein	12 (67)	Increased (>5mg) in 2.
CSF analysis/ Culture	12 (67)	All had normal analysis and negative culture.
Electroencephalogram	14 (78)	Some abnormality in 2 patients.
Brain ultrasonography	11 (61)	None had any abnormality.
Thyroid function test <sup>Ω</sup>	7 (39)	Hypothyroidism in one.
Electrocardiogram	9 (50)	Long QTc interval in an infants with hypocalcemia.
Echocardiography	2 (11)	Patent foramen ovale in both of them.
Metabolic study*	3 (17)	Normal values.
Brain CT- Scan	1 (5)	No abnormal finding.
Brain Magnetic resonance imaging	1 (5)	No abnormal finding.

ALTE: Apparent Life Threatening Event; CSF: CerebroSpinal fluid

<sup>‡</sup> Blood sugar, serum calcium, sodium, potassium, blood urea nitrogen, creatinine and in some occasion magnesium /

<sup>Ω</sup>: T3, T4, TSH / \* Ammonia and lactate

**Table 4:** Final diagnosis of neonates who presented with ALTE (n=18)

Diagnosis	Frequency (%)	Notes
Sepsis	4 (22)	Negative blood culture, but laboratory investigations were consistent with diagnosis of sepsis, i.e. elevated level of CRP or high WBC count in CBC.
Aspiration	9 (50)	Five had aspirated milk during feeding or regurgitation, whereas in one nasal secretions due to recent viral URI obstructed both nostrils. None of this group had clinical or roentgenogram evidences of pneumonia. Remaining 4 neonates according to CXR finding had evidence of aspiration pneumonia, in one, CXR showed evidences of recurrent aspirations, may be related to GERD.
Viral pneumonia	1 (5)	According to history of recent URI symptoms and contact with a sick person and CXR finding.
Hypothyroidism, Hypocalcemia and hypomagnesemia	1 (5)	The mother had hypothyroidism. The neonate had hypovitaminosis D too.
After bathing <sup>‡</sup>	1 (5)	This neonate became cyanotic and hypotonic few minutes after bathing which resolved spontaneously, no diagnosis was established.
Idiopathic	2 (11)	No diagnosis or contributing factor found.

ALTE: Apparent Life Threatening Event; CRP: C Reactive Protein; CBC: Complete blood cell count; WBC: White blood cell; URI: Upper respiratory tract infection; CXR: Chest roentgenogram; GERD: Gastro esophageal reflux disease

‡: May be considered as idiopathic

with primary diagnosis sepsis accompanied with seizure, were discharged from hospital on phenobarbital despite normal EEG and physical examination. The drug was gradually discontinued during 1 to 3 months after discharge and patients were followed for at least 6 months, had no repeated attack and appropriate developmental milestones for their age.

Table 4 shows final diagnosis of the patients. Sepsis and aspiration pneumonia were the two main final diagnoses. According to parents, ALTE was not repeated in any of the neonates during follow up period.

## Discussion

ALTEs are heterogeneous complaints which may frighten infant's caregiver<sup>[1]</sup>. ALTEs are not a diagnosis and so true attention must be paid to find the underlying diseases<sup>[6]</sup>. We aimed to offer a detailed evaluation of ALTE in the most vulnerable neonatal period in this study. In most published available studies a substantial portion of reported patients with ALTE were in the neonatal period, or at least younger than 3 months while 50% to 80% of them were younger than 2 to 3 months<sup>[2,7-9]</sup>. It is possible that infants younger than 2 months were evaluated more frequently for sepsis by the

physicians<sup>[10]</sup>. In addition, neonates or infants with recurrent ALTE were considered as high risk group with more special attention<sup>[5]</sup>.

The prevalence of ALTE in neonates presented to our ED was 11 per 1000 (1.1%) visited neonates in one year of study period. The incidence of ALTE is reported to be 1.57 to 2.46 in 1000 live births<sup>[4,11]</sup>. The difference between these reports seem to be due to the studied population and method of data collection, especially in retrospective versus prospective studies<sup>[3,4,11]</sup>.

Another explanation for the differences may be parents' perception of the episode of ALTE. In some cases the first episode did not force parents to bring their child to the hospital; however, in recurrent attacks they seek medical attention. Nearly half of our patients had more than one attack before attending the hospital, while in the other studies, prevalence of recurrent ALTE was from 12% to 44%<sup>[2,5,12]</sup>. With this high frequency of recurrent ALTEs in our population it is justified to think that many other cases of ALTE are not brought to the hospital, especially at the first episode. Interestingly boys were more frequent in our study without any definite explanation for this gender discrepancy even though in some other studies number of boys was slightly more than that of girls<sup>[7,8,11,12]</sup>, and in other studies this distribution was inverse<sup>[2,4,10]</sup>.

The youngest neonate in our study was a one day old boy who was presented after feeding.

There are some reports of ALTE in the first hours after birth due to breast feeding or a potentially asphyxiating position especially in primiparous mothers<sup>[13-15]</sup>.

Parents may be more frightened by any changes in the infants' color, especially cyanosis, that forces them to come to the hospital. In the study by Santiago-Burruchaga and his colleagues<sup>[2]</sup> cyanosis was the most common color change during ALTE among infants, the same as in ours. Fortunately death had not happened in our patients, but in one study pallor was reported more frequent in deceased patients<sup>[12]</sup>.

Many ALTE attacks last for a short time and terminate spontaneously, duration of nearly 45 to 72% of attacks was less than one minute<sup>[2,12]</sup>, and a longer duration, makes the subsequent death more probable<sup>[12]</sup>. In our study none of neonates needed resuscitation, but in other studies some infants in ALTE episode required resuscitation<sup>[2,5,10]</sup>, perhaps because most of our neonates were brought to the hospital by their parents and not by an emergency service. One important point in this situation is different reactions of parents to terminate the ALTE; non-trained parents may shake the baby, blowing to his/her face, or even taking the child upside down<sup>[11]</sup> to terminate the attack and in some severe reaction may hurt the baby. It seems important to educate basic life support to these parents before discharging the baby from hospital<sup>[16]</sup>.

It is not clear whether ALTE episodes are related to the circadian rhythm. In our study except for neonates with multiple attacks, most of them had an attack between 11 am to 11 pm in consistence with other study<sup>[2]</sup>, at the time when most of the caregivers are awake. On the other hand, as previously mentioned, most of ALTE episodes had some presentation like altered color or tone with some characteristics that caregiver must be alert and awake and observe the attack. One of the main differences between ALTE and SIDS is different in time of presentation. However, most episodes of SIDS compared to ALTE occur during night time sleep or after midnight<sup>[17]</sup>. Almost all episodes of ALTE occurred in supine position except one, and most of episodes had happened in parent's lap. We do not have definite information about infant sleep position habits in our country. But, it seems that most of neonates

sleep in supine position which is the most important factor in reducing SIDS<sup>[18]</sup>.

Owing to previous studies sepsis was one of the most important differential diagnoses in ALTE, since in one study<sup>[10]</sup> 3 of 182 infants, and in another study<sup>[7]</sup> 6 of 149 infants with ALTE had positive blood cultures. Although in our study primary impression of diagnosis was sepsis in 16 of 18 neonates, positive culture was not obtained and clinical sepsis was set up in 4 (22%) of them. Meningitis is the most dangerous infection of CNS in this age group and may present with seizure<sup>[19]</sup>. Therefore an LP was performed in most of the neonates which was negative. The rate of meningitis or any CNS infection was also very low in other studies<sup>[7,10,11]</sup>. The very low percentage of positive CNS infection was reported among positive blood cultures<sup>[7]</sup>. It seems that performing LP is not necessary for all of neonates with an episode of ALTE, especially in neonates with normal physical exam. However, recommendation of LP may be reserved for the conditions when high index of suspicion is present.

Seizure is one commonly proposed diagnosis in ALTE and thereby EEG as one of the most frequent paraclinical investigations may be normal or abnormal<sup>[7,11]</sup>. We carefully excluded neonates with probable history of seizures apart from ALTE, i.e. neonates with any abnormal movement during episode like tonic clonic, myoclonic or gaze abnormality<sup>[20]</sup> from the study. However, apnea is still one of the symptoms of seizure in infancy<sup>[1]</sup>, though apnea alone is a rare manifestation of seizure in infants<sup>[19]</sup>; in this conditions EEG monitoring is a valuable instrument in diagnosing seizure in these neonates<sup>[21]</sup>. A complete history taking, physical and neurologic examination, EEG and brain ultrasound also have been performed in the most of these patients. Four neonates were discharged from hospital with phenobarbital which was discontinued 1 to 3 months later. The attacks were not repeated and development in follow up was age appropriate. Bonkowsky et al<sup>[22]</sup> reported that 4.9% of patients with ALTE had adverse neurologic outcome, of whom 3.6% developed chronic epilepsy while most (71%) patients of this group had a second event within one month of primary ALTE regarding primary normal or abnormal EEG. Sankar and colleagues<sup>[19]</sup> advised that in the setting of normal clinical examination irrespective of EEG finding, all anti

epileptic drugs after a seizure episode may be discontinued and patient followed.

Aspiration pneumonia and viral pneumonia were one of the most final diagnoses in our patients. When a history of apnea, choking, cough or any signs of upper respiratory tract infection or close contact with a sick patient in the family was present, it is advisable to take a chest roentgenogram (CXR) to make a final diagnosis, especially in diagnosis of pneumonia. CXR was taken in all of our neonates, which was abnormal in 5 (28%). In other studies a CXR was performed in 49 to 88% of ALTE patients either neonates or infants<sup>[11,10]</sup> and in some instances nearly half of them had some abnormal findings<sup>[3]</sup>. It could be helpful in diagnosis of pneumonia, child abuse, foreign body aspiration or pleural effusion<sup>[7]</sup>.

Although it seemed that the primary attack in most of our neonates may be due to aspiration, in this age group other life threatening causes had to be ruled out initially. Milk aspiration may hasten by other co-incident factors such as nasal obstruction with secretions, tachypnea owing to pneumonia or other infections, poor feeding in septic neonates that may result in aspiration pneumonia.

After ruling out this important diagnosis, a revise in history and clinical examination and on paraclinics should be done<sup>[6]</sup>. Electrolyte measurement also remains an important part of investigation, as we had a case of hypocalcemia due to low levels of vitamin D in both mother and neonate in addition to hypomagnesaemia and hypothyroidism. The mother also had hypothyroidism. The only abnormal ECG with prolonged QTc (corrected QT interval) was seen in this neonate that resolved after administration of calcium, magnesium and supplementary vitamin D. In other studies also some cases of hypocalcemia are reported<sup>[1,7,22]</sup> and may be present with ALTE or seizure; hypocalcemia may be in differential diagnosis of ALTE in population with limited exposure to the sun light for instance mother's especial clothing<sup>[23]</sup>. Since long QTc in the first week of life has a strong correlation with SIDS, its causality with ALTE is still under question<sup>[1]</sup>. In other studies also an ECG was done for a considerable number of patients with ALTE and long QTc was not reported in their study population, meanwhile other types of heart disease were present<sup>[7,11]</sup>.

One of the most concerning issue for the parents is probability of sudden onset of the event and repetition of attacks. Though we educated parents about perfect position during feeding and sleeping time, correct feeding techniques, basic life support intervention to keep air way open, mouth to mouth breathing and chest compression. Fortunately, ALTE did not recur in our study population but these training programs make parents more confident<sup>[16]</sup>. Using home monitoring devices in this era is still controversial<sup>[6,11]</sup>.

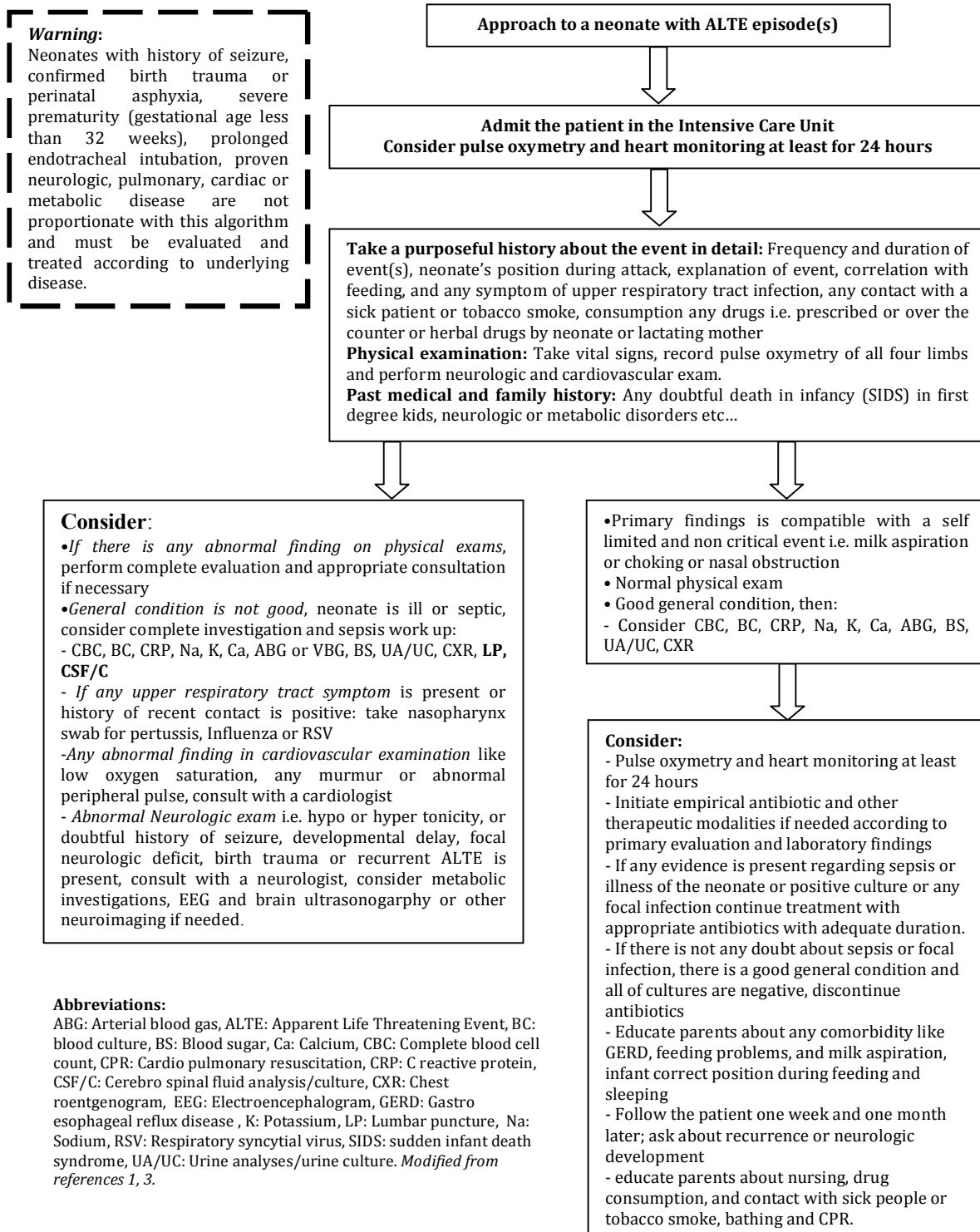
Although there is no well established guideline in managing neonates with ALTE, some institutes or authors published primary guideline to achieve a similar approach to ALTE<sup>[1,3,24]</sup>, we have designed a simple algorithm to have a similar approach to neonates presenting with ALTE (Fig. 1).

**Limitation of the study:** This study was performed in a single tertiary center in one year and so our data was not a correct estimation of prevalence or characteristics of all infants with ALTE in the community, hence significant number of these patients may not be brought to the hospital. On the other hand, small sample size in this study besides absence of a control group makes any statistical analysis of risk factors difficult or impossible. But, we tried to evaluate and followed up these neonates carefully.

## Conclusion

It seems that the rate of ALTE was more than in this report owing to high incidence of recurrent ALTEs. Although most of these attacks regress spontaneously, more attention should be paid to the underlying disease such as; infections or electrolyte imbalances. Along with a careful history, physical examination, and some basic laboratory investigation, the main causes of ALTE may be discovered. Invasive investigations like LP should be reserved for ill patients or in whom any laboratory or clinical impression of CNS infection is present. Each clinician should alarm the parents about recurrence of these episodes and train them regarding primary life support activities and abstinence from any harmful reactions.





**Fig. 1:** Algorithm for evaluation and management of neonates who presented with Apparent Life Threatening Event

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**Conflict of Interest:** None

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