Apnea in the term infant

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ABSTRACT

Whereas apnea of prematurity has been well defined and its pathophysiology extensively studied, apnea in the term infant remains a greater challenge. Unfortunately, clear diagnostic criteria are lacking and pathogenesis and management vary widely. In this review we have arbitrarily organized the discussion chronologically into earlier and later postnatal periods. In the first days of life, presumed apnea may reflect physiologic events such as positional or feeding etiologies, or may be a manifestation of serious pathophysiology, such as a seizure disorder. Beyond the neonatal period, presumed apnea may be characterized as a BRUE event (brief resolved unexplained event; formerly referred to as ALTE: apparent life-threatening event) and most frequently a precipitating event cannot be identified. Medical providers are left with somewhat of a dilemma regarding the need to hospitalize and/or work up such patients.

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1. Introduction

Apnea of prematurity is a well-described condition related to immaturity of the central and autonomic nervous systems and neurotransmitter systems. Physiologic contributors include a blunted ventilatory response to oxygen and carbon dioxide, compromised lung volumes, and small airways that are prone to collapse and obstruction. The incidence of apnea is inversely related to gestational age with the highest incidence occurring in infants ≤28 weeks of gestation. Apnea may also persist beyond 40 weeks of postmenstrual age in infants born at <28 weeks of gestation; however, this population is not included in the present discussion. Apnea in the full-term infant, which occurs at a rate of one per 1000, is not as easily understood [1].

At term an infant should be developmentally and physiologically prepared for life beyond birth, given a more mature central respiratory control network and adequate airway size and lung development. However, we have all encountered the newborn who is brought to the neonatal intensive care unit (NICU) after turning blue when attempting to breastfeed, or the baby who is transferred from a referral hospital for apnea and cyanosis appreciated for the first time on or near the day of discharge. Later in infancy, the parents may witness a brief resolved unexplained event (BRUE), formerly known as an apparent life-threatening event (ALTE), prompting an emergency call or a visit to the emergency department. These scenarios suggest that there is either underlying pathology causing apnea, or that what is perceived as apnea is not truly apnea. However, even a term infant does not have a robust respiratory control network and remains vulnerable to a variety of environmental stressors, especially within the first six months of life. In this article we address the challenge of defining apnea in the term infant, identify the many causes of apnea at term, highlight developmental changes in respiratory control, and review the topic of BRUE. The discussion will be organized chronologically into the early neonatal period (0–3 days of life) and the later neonatal period, extending into infancy (>3 days to 1 year).

2. Definition of apnea

The standard definition for pathologic apnea is a cessation of respiratory effort or airflow for ≥20 s or of shorter duration when accompanied by bradycardia or hypoxemia. This time-honored definition, however, is not evidence-based and lacks parameters for the degree of bradycardia or hypoxemia required to make it clinically significant [2]. In a study published in 1969 describing the use of transthoracic impedance monitoring, the apnea alarm limit was arbitrarily set at 20 s and the authors concluded that apnea of about 20 s duration was the "non-breathing interval which [a larger preterm infant] cannot tolerate without bradycardia and cyanosis"

[3]. The landmark CHIME study evaluated cardiorespiratory events in both term and preterm infants who were monitored at home. An "extreme apnea" was arbitrarily defined as an event lasting ≥30 s. The home apnea monitors that were used applied standard apnea alarm thresholds of 20 s for most of the infants and 40 s for the healthy term group [4]. To date, there is no consensus definition for a clinically significant respiratory event based on pause duration alone, let alone at term.

Apnea may be central, obstructive, or mixed. Mixed apnea (a period of central apnea, typically followed by airway obstruction) is the most frequent type of longer apnea in preterm infants. Presumably apnea in term infants may also be central or have an obstructive component.

Whereas apnea of prematurity is a consequence of immature physiology and development that spontaneously resolves by 40–44 weeks of postmenstrual age, apnea in term infants is more likely to be pathologic and require a detailed evaluation and the consideration of a long list of possible causes.

3. Apnea from birth to three days

The Textbook of Neonatal Resuscitation, 7th edition, addresses apnea at birth in the context of an indication for positive pressure ventilation [5]. There are many recognized conditions that present with apnea in the delivery room, including brain injury from hypoxia and ischemia (when associated with hypotension, hypoxemia, and metabolic acidosis), intrapartum maternal drug (e.g. narcotic or magnesium) administration, or general anesthesia and early onset sepsis. Other conditions presenting with central apnea in the early neonatal period are congenital central nervous system malformations, seizures secondary to ischemic infarction or stroke, temporal lobe lesions, metabolic causes (abnormalities in glucose, electrolytes, calcium), traumatic brain injury, intracranial hemorrhage, and inflammation secondary to pneumonia, sepsis, or meningitis. Pro-inflammatory cytokines, such as interleukin-1β (IL-1β), are known triggers for central apnea and problems with respiratory control. IL-1β has been identified as the cause of many systemic and local inflammatory disorders including inflammation of the brainstem. There is additional information demonstrating that IL-1β exerts its effects on the brainstem via prostaglandin E$_2$ (PGE$_2$). Transient hypoxia has also been shown to increase brainstem microsomal prostaglandin E synthase-1, and PGE$_2$ levels. Both PGE$_2$ and its metabolite have been implicated in depression and dysregulation of the central cardiorespiratory control networks. Inflammation and hypoxia, in combination, could significantly impair the ability of an infant to auto-resuscitate, potentially resulting in death [6,7].

Soon after birth, despite a successful transition and uncomplicated perinatal course, an infant may be found apneic, cyanotic, or in asystole. Poets et al. investigated the incidence of unexplained and sudden unexpected infant death (SUID) and severe apparent life-threatening event (ALTE) in the first 24 h of life in pediatric departments in Germany over a one-year period. The incidence of SUID and ALTE was 2.6 per 100,000 live births. Placing infants in a potentially asphyxiating position was identified as the greatest risk factor [8]. A case series from France described six cases of ALTE in the delivery room in the first 2 h of life. In each instance the infant was prone on the mother's abdomen during early skin-to-skin contact and most of the mothers were primiparous [9]. These publications emphasize the importance of close observation of the mother–infant dyad following delivery. The American Academy of Pediatrics' Committee on Fetus and Newborn published a clinical report in 2016 offering guidance to delivery hospitals and birthing centers for establishing appropriate skin-to-skin care (SSC) and safe sleep policies in order to avoid sudden unexpected postnatal collapse (SUPC) [10]. SUPC is defined as an unexpected collapse leading to death, NICU admission, or encephalopathy within the first seven days of life in a term or late preterm infant who appeared well at birth. As with sudden infant death syndrome (SIDS), it is a diagnosis of exclusion. The incidence is estimated to range widely from three to 133 cases per 100,000.

Term and late preterm infants may occasionally be challenged by the introduction of oral feeds and breathing may be compromised. Studies performed in bottle-fed infants several decades ago demonstrated that some vigorously sucking infants swallow with each suck, which can occur up to 30–60 times per minute. There is protective upper airway closure with each swallow, thus consequently hypoventilation, apnea, and cyanosis may result.

Obstructive apnea may occur from congenital or acquired airway obstruction, including anomalies of the upper airway, craniofacial abnormalities, functional causes of obstruction from laryngomalacia, vocal cord paralysis or paresis, phrenic nerve injury, and stimulation of the laryngeal chemoreflex from reflux or problems with coordination of sucking, swallowing, and breathing as mentioned above. Syndromes with clinical features of oropharyngeal airway obstruction include the Pierre Robin sequence, Treacher Collins syndrome, Goldenhar syndrome, Crouzon disease, and Down syndrome.

Congenital central hypoventilation syndrome (CCHS) should also be considered when evaluating an apparently otherwise healthy newborn with apnea and cyanosis. CCHS was first described by Mellins in a case report from 1970. The male infant described in the report was noted to be cyanotic on admission to the nursery, during sleep and with feedings. Hypothermia and esophageal dysmotility were also present. Since then, Hirschsprung disease, constipation, and tumors of neural crest origin were added to the constellation of findings in these patients. Currently, CCHS is defined as a severe manifestation of respiratory and autonomic nervous system dysregulation involving other multiple organ systems including cardiac, sudomotor, ophthalmologic, neurologic, and enteric. At the turn of the twenty-first century, mutations in the PHOX2B gene were identified as disease-defining for CCHS [11]. The diagnosis may be delayed until after the newborn period and should be included in the differential diagnosis for central apnea presenting in the first year of life. Box 1 is a summary of possible causes of apnea in the first three days of life.

4. Apnea in later infancy, from more than three days to one year

During the first six months of life, the healthy term infant continues to undergo myelination and maturation of the central nervous system and developmental changes in peripheral chemoreceptor response to oxygen and carbon dioxide. The respiratory pattern that best reflects these maturational changes is periodic

Box 1
Considerations for apnea presenting in first days.

Perinatal events, e.g. drugs, hypoxia–ischemia, sepsis
Metabolic causes
Central nervous system abnormalities, e.g. trauma, hemorrhage, congenital anomalies, seizures
Unexplained, e.g. positional
Feed-related hypoventilation/apnea
Upper airway obstruction
Congenital central hypoventilation

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breathing (PB). PB is characterized by cycles in which a few breaths of 5–10 s alternate with periods of apnea of a similar duration. PB, absent in the first few days of life, becomes frequent at 2–4 weeks of age, and is rare by six months [12]. PB occurs predominantly during quiet sleep. Kelly et al. analyzed pneumographic recordings in 123 term infants during the first 12 months of life. They found that periodic breathing decreased significantly over time from 78% at 0–2 weeks to 29% at 39–52 weeks. None of the infants had apnea greater than 15 s or bradycardia [13]. The healthy term control group in the CHIME Study had frequent conventional apnea events of ≥20 s, but events >30 s were rare [4]. Brockmann et al. performed overnight unattended polygraphies in the homes of 37 healthy term infants to obtain reference respiratory values for babies <3 months of age. Nasal flow, inductance plethysmography, snoring, pulse oximeter-derived arterial oxygen saturation, pulse waveform, and electrocardiogram were recorded. Short central apneas (<20 s) and periodic breathing were frequent, obstructive apneas were rare, and desaturation events ≤3% from baseline were frequent. No bradycardia (<50 bpm for ≥5 s or <60 bpm for ≥15 s) was observed [14]. It would appear that the dynamic changes occurring in the brain and peripheral chemoreceptor systems of healthy term infants could render them at risk for apnea during the first postnatal months. However, improved lung function and greater oxygen reserves make them less vulnerable to significant desaturation and/or bradycardia. A single center reviewed their experience with infants diagnosed with obstructive sleep apnea (OSA) by polysomnography. They found that the causes of OSA in infancy were different than those found in older children. Gastroesophageal reflux (GER) was identified in 30%, laryngomalacia in 24%, and craniofacial anomalies in 16%. Genetic conditions were identified in 53%, most frequently trisomy 21 [15].

Gastroesophageal reflux has long been implicated as a cause of apnea in infancy. In a 2014 systematic review to determine the association between GER and apnea, only one study found a significant increase in apnea following GER. The authors concluded that there is insufficient evidence to confirm an association between GER and apnea [16]. Moreover, there is no standard for the window of time between reflux and apnea events that defines a temporal association. In our Infant Respiratory Program, where we use multi-channel intraluminal impedance (MII)–pH probe monitoring in conjunction with respiratory inductance plethysmography, electrocardiography, and pulse oximetry, we have identified patients in whom reflux precedes a cardiorespiratory event within a window of <1 min. Our patient population consists of former preterm infants with persistent bradycardia with or without clinical reflux and term infants admitted for ALTE. Nunez et al. described a series of former preterm infants (≤29 weeks of gestation) with persistent cardiorespiratory events and clinical reflux between 39 and 48 weeks of corrected age, who were being evaluated for possible fundoplication. An association between MII events and obstructive apnea was found in three patients [17]. The challenge with bringing further clarity to the reflux–apnea association in healthy term infants is based on the fact that GER in infancy is frequent and central or obstructive apnea is relatively rare. Any association between the two may occur as a result of chance.

The most frequent presentation of what might appear to be apnea is an ALTE, which, in 2016, was replaced by the acronym BRUE [18]. The terminology for this "condition" has undergone three revisions over the last 30 years. In the 1980s the phrase "near-miss SIDS" was used to describe these infants until it was recognized that SIDS is a unique phenomenon not necessarily related to apnea. The 2016 clinical practice guideline for BRUE follows a previous systematic review published by Tieder et al. to evaluate the historical and physical exam features of a "serious" ALTE and determine what testing is necessary [18,19]. The rationale for this change in terminology is to stratify, by risk, infants who are likely to have a recurrent event or serious underlying disorder from those who are lower risk. The bulk of the report provides diagnosis and management guidelines for babies in the lower risk category. The clinical criteria for BRUE have also been revised from those used to define ALTE. A BRUE is an event occurring in infants <1 year of age with one or more of the following: (i) cyanosis or pallor; (ii) absent, decreased, or irregular breathing; (iii) marked change in tone (hyper- or hypotonia); and (iv) altered level of responsiveness. The diagnosis of BRUE should only be applied when there is no explanation for a qualifying event after a thorough history and physical examination. Low risk infants are defined by: (i) > 60 days of age; (ii) gestational age ≥32 weeks and ≥45 weeks of postconceptional age; (iii) event duration <1 min; (iv) no CPR (provided by trained medical personnel); (v) no "concerning" historical features (specified in the clinical practice guideline in detail); (vi) no concerning physical findings (also specified). These guidelines provide a number of significant benefits for the emergency physician who is often involved in the triage of these patients. One of the most important elements of the guidelines is the removal of the caregiver's perception that the event was "life-threatening." Instead, the nature of the episode is determined by the clinician after a comprehensive history and physical examination. Another significant change is that choking or gagging is not included in the definition of BRUE (a frequent observation cited by families for ALTE). Finally, hospitalization for cardiorespiratory monitoring is discouraged for the lower risk patient.

The list of medical conditions that are not consistent with BRUE or that place an infant in a higher risk category are listed in Box 2.

In an effort to characterize esophageal motility in infants with the diagnosis of an ALTE, Hasenstab et al. compared pharyngoesophageal manometry in healthy term infants and those with proven ALTE. In the infants with ALTE, prolonged spontaneous respiratory events were associated with ineffective esophageal motility. The authors suggest that it is more likely an abnormality in swallow–respiratory junction interactions than gastroesophageal reflux that is responsible for spontaneous prolonged respiratory events in these patients [20].

We retrospectively reviewed the disposition of ALTE patients over a 6-year period (2010–2015) who were admitted to our center

Box 2
Serious conditions presenting with BRUE (brief resolved unexplained event)-like symptoms.

Gastroesophageal reflux
Respiratory tract infection [respiratory syncytial virus]
Seizure or central nervous system disorder
Child abuse
Other
  Poisoning
  Bilirubin encephalopathy
  Cardiac disease
    Structural
    Conduction or ion channel (channelopathies) defects
    Cardiomyopathies
    Arrhythmias
Metabolic disorders/inborn errors of metabolism
Anaphylaxis
Bacterial infections (including urinary tract infection)
Upper airway obstruction/obstructive sleep apnea
Anemia

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and had a 12 h pneumogram with combined pH/MII study performed. All patients were ≥37 weeks of gestation. Of the 90 infants studied, 35 had feeding interventions that included a change in formula, thickened feedings, positioning, nasogastric tube feedings, change in nipple type, and pacing of feedings; 30 had no intervention; 20 were treated with gastrointestinal drugs (proton pump inhibitors, H_2 blockers, and metoclopramide); 12 were discharged on home apnea monitors; and 10 were identified with underlying conditions. Eleven infants received more than one intervention, often a combination of a gastrointestinal medication with a change in feeding strategy (Fig. 1).

It is evident both from the ALTE/BRUE literature and our own data that feeding, esophageal motility, and gastrointestinal events are responsible for the majority of perceived cardiorespiratory episodes in infancy and that true isolated apnea is actually very rare.

Respiratory syncytial virus (RSV) infection has been associated with apnea in infancy. The incidence of apnea associated with bronchiolitis ranges from 1% to 24%. In a prospective multi-centered study a corrected age of <2 weeks, <2—8 weeks of age, birth weight <2300 g, and previous history of apnea were significant independent predictors for RSV-related apnea. The severity of the pre-admission respiratory status also placed an infant at increased risk [21]. Not surprisingly, the mechanisms for apnea in RSV appear to lie within the autonomic nervous system. In eight infants <2 months of age presenting with apnea during RSV infection, non-invasive electrophysiologic monitoring demonstrated profound central autonomic nervous system dysfunction as indicated by lower heart rate variability and baroreflex components [22]. However, it should be noted that the apnea attributable to RSV is low (<1%) in previously healthy term infants [23]. Apnea is a frequent finding in *Bordetella pertussis* infection and the incidence has increased in the USA. In a prospective cohort study to determine the prevalence of *B. pertussis* in children aged <2 years hospitalized with bronchiolitis, pertussis was found to be a rare pathogen. Apnea occurred in 10% of the infants with probable pertussis but in none with confirmed infection [24]. In a population of children with pertussis requiring admission to a pediatric intensive care unit in Auckland, New Zealand, 97% were aged <1 year and apnea or paroxysmal cough was present in 46% [25].

A number of inborn errors of metabolism, including mitochondrial disease, Pompe disease, Leigh syndrome, and the mucopolysaccharidoses, may present with central or obstructive apnea as a manifestation of acute metabolic encephalopathy or airway compromise.
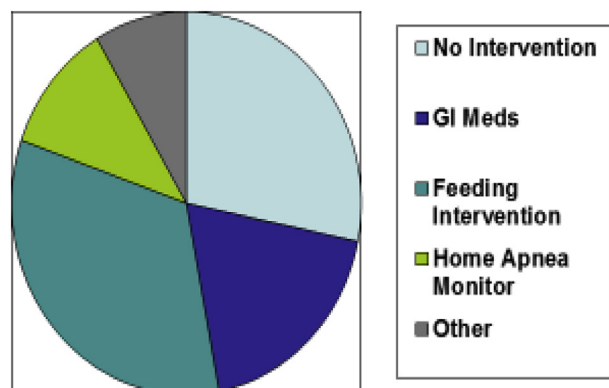
5. Evaluation and management

Obtaining a thorough history and performing a detailed examination is essential to the evaluation of a term infant presenting with apnea. In the first three days of life, a careful review of the maternal, prenatal, intrapartum, resuscitation, and postpartum history may yield important clues. A thorough feeding history is imperative in all cases. Laboratory studies should include glucose, electrolytes, calcium, complete blood count, and blood gas determinations. A period of observation with cardiorespiratory and pulse oximetry monitoring in a NICU is recommended. Neuroimaging, electroencephalogram, ear—nose—throat consultation, and a genetics evaluation should be considered based on the infant's history, clinical course, and physical findings. For infants who present outside of the early neonatal period, attention to the 2016 BRUE Clinical Practice Guideline is advised. This will guide further evaluation and need for hospitalization. Speech or occupational therapy may be consulted to address feeding-related issues. Studies evaluating the efficacy of methylxanthine therapy as a treatment for apnea secondary to RSV have shown no clear benefit [26]. Given the mechanism of action for caffeine in apnea of prematurity and the many possible causes for apnea at term, caffeine cannot be recommended for this patient population. A more suitable approach is to identify an underlying cause, if possible, and target management accordingly. Prevention strategies to encourage safe SSC and rooming-in practices, as well as parent education regarding safe sleep, should also be implemented. A pneumogram or polysomnogram may be helpful to characterize the nature of persistent cardiorespiratory events in hospitalized patients when an underlying cause cannot be identified.

5.1. Practice points

- Apnea in the term infant is an unusual occurrence that requires consideration of a number of etiologies depending on whether it is central or obstructive and the age at presentation, early (<3 days) versus later (>3 days to 1 year).
- The diagnosis requires a thorough history and physical examination with the potential need for a period of observation and monitoring. Laboratory studies include electrolytes, blood glucose, complete blood count, and blood gas determination. A more detailed neurologic evaluation, pneumogram, or polysomnogram may also be necessary.
- A brief resolved unexplained event (BRUE) has specific diagnostic criteria and is not synonymous with apnea. The decision of whether or not to hospitalize such an infant is dependent on identifying the patient as lower versus higher risk.

5.2. Research directions

- Develop a definition for clinically significant apnea in the term infant based on pause duration alone through better understanding of basic respiratory physiology.
- Create standardized investigations of ALTEs that occur during the first few hours of life to identify risk factors.
- Clarify the use of the BRUE nomenclature from epidemiologic, diagnostic, and pathophysiologic perspectives.

Fig. 1. Disposition of ALTE (apparent life-threatening event) admissions: 2010—15. GI, gastrointestinal.

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