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Apnea in the term infant

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A B S T R A C T

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.

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"

Abbreviations: BRUE, brief resolved unexplained event; ALTE, apparent life-threatening episode; SIDS, sudden infant death syndrome; SUID, sudden unexplained infant death.

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[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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