



## Sleep related breathing disorders and indications for polysomnography in preterm infants

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### ABSTRACT

There is a range of breathing problems which occur and may persist in preterm infants, such as central apneas, obstructive apneas and periodic breathing. Preterm infants may also suffer from respiratory distress syndrome and chronic lung disease necessitating prolonged use of oxygen therapy after discharge from the hospital. Due to these persistent breathing pattern abnormalities in preterm infants, there is a higher risk of altered sleep and apparent life threatening events. Polysomnography can be a helpful tool to identify those infants who have abnormalities in their breathing pattern, to identify those infants who have an increased risk to get a sleep related breathing event at home and to decide about the discontinuation of oxygen therapy.

### 1. Introduction

Sleep is very important for the optimal development of children, but is also a state in which breathing difficulties are most prominent. Preterm infants have a known risk of an immature breathing pattern or apnea of prematurity which may lead to bradycardias and desaturations both awake and while asleep. Invasive or non-invasive respiratory support or pharmacologic treatment with methylxanthines, such as caffeine or with doxapram is necessary to overcome these problems in many preterm infants [1–4]. Compared with term infants, prematurely born infants have a blunted response to a hypercapnic challenge, a diminished glossopharyngeal muscular contraction in response to periodic breathing, and a higher percentage of events due to poor sucking and swallowing that result in apnea when attempting to oral feed [5]. Furthermore, infants with persistent apnea or bradycardia may have delayed maturation of these physiologic skills and there is also a close relation between coordination of sucking and cardiorespiratory control [5,6]. Breathing problems may also occur due to a lack of tone in the upper airway, followed by collapse and obstruction. Many preterm infants will suffer from infant respiratory distress syndrome (IRDS), necessitating respiratory support or treatment with surfactant [7].

Most of the preterm infants will develop a mature breathing pattern and recover from the initial lung disease. However, in a number of preterm infants breathing problems can persist and can be related to inadequate maturation of the breathing pattern, obstructive breathing or the development of a chronic lung disease [8–10]. Furthermore, preterm infants are at increased risk for an apparent life-threatening event (ALTE) or brief resolved unexplained event (BRUE) [11,12]. Most of these breathing problems occur during sleep. The presence of breathing problems or unexplained events, usually leads to a stay in the hospital setting until the child has normal control of breathing during sleep. Polysomnography is a helpful tool to analyze these breathing problems. In this review we will describe the indications for the different clinical entities to perform sleep studies (polysomnography) and the consequences for further treatment and follow-up.

### 2. Polysomnography

#### 2.1. General

Polysomnography (PSG) is a versatile diagnostic tool that is being increasingly used to diagnose and monitor several diseases and conditions in children [13,14]. The most commonly known use of PSG is diagnosing and monitoring sleep-disordered breathing (SDB), since it is the gold-standard method [15,16]. During full level 1 overnight video-PSG, a number of physiological signals are recorded. This includes electroencephalography (EEG), electro-oculogram, submental and leg electromyogram, oronasal airflow, abdominal and chest wall movements, pulse oximetry, partial pressure of end-tidal or transcutaneous carbon dioxide, and a video-recording [13,14].

#### 2.2. Polysomnography in preterm infants

Cardiorespiratory monitoring is a key feature of contemporary neonatal intensive care. It enables the clinician to provide the best care for even the most preterm infants of 24 weeks' gestational age. Heart rate variability and general movement characteristics may serve as predictor for

**Table 1**  
Definitions of breathing abnormalities (according AASM criteria [67]).

Central apneas	Absence of inspiratory effort throughout the event $\geq 20$ s in duration, or the event is associated with an arousal or $\geq 3\%$ oxygen desaturation; or only in infants $< 1$ year of age: the event is associated with a decrease in heart rate to $< 50$ beats/min for at least 5 s or $< 60$ beats/min for 15 s.
Obstructive apnea	The event lasts for at least 2 missed breaths and is associated with a $> 90\%$ fall in the signal amplitude for $\geq 90$ of the entire respiratory event compared to the pre-event baseline amplitude.
Hypopnea	Peak signal excursions drop is $\geq 30\%$ of pre-event baseline for $\geq$ the duration of 2 breaths in association with either $\geq 3\%$ oxygen desaturation or an arousal.
Oxygen desaturation	A decrease oxygen saturation of $\geq 3\%$ .
Hypoventilation	Transcutaneous or end-tidal $\text{CO}_2$ : at least 25% of total sleep time $> 50$ mm Hg (= 6.7 kPa).
OSAS	An obstructive AHI $\geq 2$ episodes/h or an obstructive apnea index $\geq 1$ episode/h in the presence of SDB symptoms, adenotonsillar hypertrophy with or without obesity and no other abnormalities.
OSAS classification	Mild OSAS: obstructive AHI of 2–5 episodes/h Moderate-to-severe OSAS: obstructive AHI $> 5$ episodes/h.
Periodic breathing	$> 3$ episodes of central apnea lasting $> 3$ s separated by no $> 20$ s of normal breathing.

morbidity, mortality and neurodevelopmental outcome [17,18]. Nowadays, EEG and cardiorespiratory monitors can be used to evaluate sleep and sleep states in very small preterm infants [19,20]. PSG recording in the NICU is technically challenging, especially in smaller neonates. No international guidelines are available on timing of PSG in preterm infants. Very few studies have performed PSG in very low birthweight infants [21,22]. Performing full level 1 overnight video-PSG has some important limitations in preterm infants, since the stickiness of the recording electrodes can damage the fragile skin [20,23] and the PSG equipment will give a lot of disturbance and interferes with the newborn individualized developmental care and assessment program (NIDCAP) guidelines for the sick preterm infant [24]. In a research setting, PSG can be performed in the neonatal intensive care unit (NICU) when an infant reaches the arbitrary age of 35 weeks' postmenstrual age (PMA) or when it is stable enough [25–28]. More feasible might be to perform a PSG near term equivalent age, commonly prior to discharge [8].

### 3. Indications for polysomnography in preterm infants

#### 3.1. Immature breathing pattern/persistent apnea of prematurity

Apnea of prematurity is a common developmental disorder occurring in preterm infants [29]. It is a consequence of immaturity of the brainstem and peripheral chemoreceptors [30,31]. A preterm infant younger than 37 weeks' gestation is generally considered to be suffering of apnea of prematurity if it suffers apneas of  $> 20$  seconds' duration, or a shorter respiratory pause accompanied by bradycardia or hypoxia (Table 1). The incidence of apnea of prematurity is inversely related to gestational age. Virtually all preterm infants of a gestational age  $< 28$  weeks suffer from apnea of prematurity. In most infants, the symptoms resolve around 37 weeks' postmenstrual age (PMA).

Distinct from apnea of prematurity, periodic breathing is a normal immature breathing pattern for neonates and occurs in term as well as preterm infants. It appears in the second week after birth, peaks at several weeks of age, then decreases, but may continue for up to six months or longer [32]. Excessive periodic breathing ( $> 10\%$  of sleeping time) or an abrupt increase over prior baseline may reflect illness or physiological stressors, or may occur without any apparent clinical event. Nonetheless, its occurrence warrants consideration for potential pathology. Also, studies have reported increased cardiorespiratory events in preterm infants after immunizations, which might be related to periodic breathing. Others, however, have not found this association, which may reflect different maturational stages and clinical entities [33–35].

In many cases, occasional apneas or the possibility of an apnea may delay discharge from the hospital. The required apnea-free period needed before an infant can be discharged remains controversial. Clinicians typically assess maturation of respiratory control in relation with feeding behavior through observation of infants in the hospital with a duration varying between 1 and 21 days. In a retrospective study of 1403 infants with an average gestational age of  $31.1 \pm 2.6$  weeks and an average PMA at discharge of  $35.6 \pm 1.8$  week, the success rate and event identification rate for a specific apnea- or bradycardia-free interval was studied. Only those infants were studied who were ready-for-discharge and free from the last apnea or bradycardia event for 21 days; 84.2% did not have an apnea event and 78.5% did not have a bradycardia event. For the entire cohort, a 95% success rate was statistically reached, with a 7-day apnea- or bradycardia-free interval [5]. A higher success rate was found when the analysis was restricted to infants who were off methylxanthines for 3 or 5 days. Discontinuation of routine caffeine treatment was also studied in 95 preterm infants, and it was shown that after discontinuation a substantial number of hypoxic events persisted, but with increasing PMA these progressively decreased [36]. Extended caffeine treatment until 40 weeks' PMA decreased the number of hypoxic events.

Fairchild et al. provided a quantitative analysis of central apnea throughout the NICU stay of 1211 preterm infants born  $< 35$  weeks' gestation and concluded that NICU discharge was safe after a week free of needing stimulation to resolve an apneic spell, since most infants were being sent home without a monitor and very few, namely 4.7% were readmitted within 2 months for an apnea or ALTE [37].

Some infants, however, continue to suffer from cardiorespiratory events. If apneas persist, other possible diagnoses must be excluded, for example central nervous system pathology. In rare cases, the congenital central hypoventilation syndrome (CCHS), or Ondine's curse, can be the cause of persisting apneas in infants [38]. The occurrence of apnea/bradycardia events after discharge from the hospital was studied in  $> 1000$  preterm and healthy term infants who were monitored at home. Extreme events, such as apnea  $> 30$  s and/or heart rate  $< 60$  beats per minute for  $> 10$  s, were very rare but were observed most frequently in former preterm infants and the occurrence decreased until about 43 weeks' PMA [39].

In none of the studies described above, PSG was used to investigate the respiratory control in these preterm infants. Events were captured either through a nursing report in the medical chart [5], quantitative analysis of central apneas [40], or by home monitoring devices [39]. Only in a few studies polysomnography has been done in preterm infants before discharge from the hospital [8]. Daniëls et al. performed overnight polysomnography before discharge at a postmenstrual age of 36–40 weeks in 1274 preterm born infants with a gestational age  $< 34$  weeks at birth and the findings were compared with data obtained subsequently from home documented monitoring [8]. It was found that 162 (12.7%) infants still had central apneas ( $> 15$  s) and 34 (2.7%) a bradycardia ( $< 50$  bpm for a minimum of 4 s) and/or severe obstructive apnea for  $> 15$  s with bradycardia  $< 60$  bpm, with oxygen desaturation  $< 80\%$ . In follow-up, 19 out of 34 of these preterm infants had subsequent documented life threatening events caused by a central or obstructive apnea, with bradycardia varying from 12 to 41 bpm during home monitoring, but none of the children with

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