Obstructive Sleep Apnea in Infants

Eliot S. Katz¹, Ron B. Mitchell², and Carolyn M. D'Ambrosio³

¹Division of Respiratory Diseases, Department of Medicine, Children's Hospital, and Harvard Medical School, Boston, Massachusetts; ²Department of Pediatric Otolaryngology, University of Texas Southwestern Medical Center, and Children's Medical Center, Dallas, Texas; and ³Division of Pulmonary Diseases, Department of Medicine, Tufts Medical Center and Tufts Medical School, Boston, Massachusetts

Obstructive sleep apnea in infants has a distinctive pathophysiology, natural history, and treatment compared with that of older children and adults. Infants have both anatomical and physiological predispositions toward airway obstruction and gas exchange abnormalities; including a superiorly placed larynx, increased chest wall compliance, ventilation-perfusion mismatching, and ventilatory control instability. Congenital abnormalities of the airway, such as laryngomalacia, hemangiomas, pyriform aperture stenosis, choanal atresia, and laryngeal webs, may also have adverse effects on airway patency. Additional exacerbating factors predisposing infants toward airway collapse include neck flexion, airway secretions, gastroesophageal reflux, and sleep deprivation. Obstructive sleep apnea in infants has been associated with failure to thrive, behavioral deficits, and sudden infant death. The proper interpretation of infant polysomnography requires an understanding of normative data related to gestation and postconceptual age for apnea, arousal, and oxygenation. Direct visualization of the upper airway is an important diagnostic modality in infants with obstructive apnea. Treatment options for infant obstructive sleep apnea are predicated on the underlying etiology, including supraglottoplasty for severe laryngomalacia, mandibular distraction for micrognathia, tonsillectomy and/or adenoidectomy, choanal atresia repair, and/or treatment of gastroesophageal reflux.

Keywords: sleep-disordered breathing; adenotonsillar hypertrophy; craniofacial; micrognathia; laryngomalacia

Infants experience a wide range of sleep-disordered breathing patterns, including periodic breathing (1), apnea of prematurity (2), and central apnea, but little attention has been given to obstructive sleep apnea (OSA). Infants are particularly vulnerable to obstructive sleep-disordered breathing related to their upper airway structure (3), adverse pulmonary mechanics (4), ventilatory control (5), arousal threshold (6), laryngeal chemoreflex (7), and an REM-predominant sleep state distribution (8). The anatomical and physiological predispositions toward airway obstruction in infants are summarized in Table 1. Airway collapse may occur passively related to the balance between the viscoelastic properties of the pharynx, pharyngeal dilators, and the transmural pressure. Alternatively, obstructive apnea may result from active glottic closure, termed the *laryngeal chemoreflex*. The diagnosis of OSA in infants is confirmed by polysomnography and the etiology is often determined via direct endoscopic visualization

of the airway. Infants with severe OSA will often have marked hypoxemia or sleep fragmentation, which is likely to result in considerable morbidity. As such, successful therapy is mandatory, even if this requires invasive treatment including nasopharyngeal tubes, continuous positive airway pressure (CPAP), supraglottoplasty, or even tracheostomy. This review focuses on the clinical features, polysomnographic patterns, pathogenesis, diagnosis, and management of OSA in infancy.

OVERVIEW

The determinants of upper airway stability include anatomical structure, neuromuscular activation of airway dilators, ventilatory control, and the arousal threshold from sleep. During wakefulness, laryngeal and pharyngeal dilator muscles actively sustain airway patency and a stable breathing pattern is maintained. The infant may appear to have labored breathing and stridor, but frank obstructions and gas exchange abnormalities are typically absent unless there is comorbid neuromuscular weakness or marked upper airway narrowing. At sleep onset, there is a reduction in airway and respiratory muscle activity, as well as the emergence of an apneic threshold to CO₂ that is approximately 1 mm Hg below eupneic levels. As sleep progresses, there is a gradual recruitment of upper airway dilator muscles and increased respiratory drive in response to hypercapnia and negative luminal pressure. Stable breathing is intermittently achieved provided that the increase in respiratory drive, hypercapnia, and negative luminal pressure remain below the infant's arousal threshold. Sudden airway opening, as seen during an arousal, promotes a ventilatory overshoot that lowers CO₂ below the apneic threshold, thus initiating obstructive cycling. The specific determinants affecting the clinical expression of OSA in infants are discussed in more detail below.

ANATOMY OF THE INFANT AIRWAY

Increased upper airway resistance during sleep is an essential feature of OSA in infants. Airway narrowing may result from congenital or acquired abnormalities occurring from the nose to the larynx. The newborn's face is approximately 40% of the adult size, and increases to 65% by 3 years of age. Facial growth is determined by both genetic and functional factors, but most importantly by the route of breathing. At birth, there is a disparity in craniofacial development with the cranium being the most mature, the maxilla intermediate, and the mandible being the least developed. Airway obstruction may be related to skeletal anomalies, soft tissue enlargement, or a combination of both.

Nose

The newborn trachea and larynx are relatively superiorly positioned, resulting in a close proximity between the epiglottis and soft palate. Teleologically, this configuration facilitates the

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Correspondence and requests for reprints should be addressed to Eliot S. Katz, M.D., Division of Respiratory Diseases, Mailstop 208, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115. E-mail: eliot.katz@childrens.harvard.edu

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TABLE 1. PREDISPOSING FACTORS AND MEDICAL CONDITIONS ASSOCIATED WITH INFANT OBSTRUCTIVE SLEEP APNEA

Craniofacial
Maxillary hypoplasia
Craniosynostosis (152, 153)
Apert
Crouzon
Pfeiffer
Muenke
Saethre-Chotzen
Achoondroplasia (154)
Down's syndrome (155)
Treacher Collins
Micrognathia
Nonsyndromic Robin sequence (119)
Syndromic Robin sequence (Stickler, Treacher Collins) (119)
Nager syndrome (156)
Hemifacial microsomia (157)
Macroglossia
Beckwith-Wiedemann (158)
Down's syndrome (155)
Hemangioma, lymphangioma
Achoondroplasia (154)
Laryngeal
Laryngomalacia (32)
Vocal cord paralysis (159)
Laryngeal edema (160)
Congenital subglottic stenosis (122)
Acquired subglottic stenosis
Laryngeal web/cysts
Hemangiomas
Neurological
Cerebral palsy (161)
Chiari malformation (159)
Spinal muscular atrophy (162)
Mitochondrial disorders (163)
Nasal obstruction
Choanal atresia (164)
Pyiform aperture stenosis (165)
Nasolacrimal duct cysts (166)
Upper respiratory infection
Nasogastric tube
Septal deviation
Allergic rhinitis
Respiratory mechanics/ventilatory control
High chest wall compliance
Rib configuration round/horizontal
Small diaphragmatic zone of apposition
High metabolic rate
NREM apneic threshold close to eupneic CO ₂ level
Ventilation-perfusion mismatch
Miscellaneous
Prader-Willi syndrome (93)
Mucopolysaccharidoses (167)
Gastroesophageal reflux (22)
Obesity (90)
Adenotonsillar hypertrophy (generally >6 mo of age) (83)
Maternal smoking during gestation (87)
Increased REM sleep
Neck flexion
Respiratory Infection
Sleep deprivation
Sedatives

Definition of abbreviation: NREM = non-rapid eye movement.

partitioning of the pharynx to optimize suckling. However, this anatomy also confers a strong preference toward nasal breathing in infants. Thus, spontaneous mouth breathing during sleep is observed in only 30% of infants, and nasal breathing remains the primary route at all times (9). Further, nasal occlusion challenges in infants result in a switch to mouth breathing in only 40% of infants, and this requires arousal from sleep, oxygen desaturation, and/or audible grunting (9). The switch to mouth breathing is less

effective during REM sleep and in younger infants (10, 11). Nasal resistance in infants is responsible for 50% of the total upper airway resistance, and may further increase as the result of secretions, transnasal tubes, mucosal edema, and vascular engorgement. Consequently, obstruction of the nasal passages, resulting from skeletal, soft tissue, upper respiratory infection (12), or iatrogenic causes, may result in OSA in infants (see Table 1). Complete nasal obstruction, as seen in choanal atresia, has been reported to result in cyanosis and rarely death in infancy.

Mandible

The infant mandible is nearly horizontal at birth, with a short ramus and flexible temporomandibular ligament, resulting in a propensity toward posterior displacement. During early fetal development, mandibular hypoplasia results in tongue displacement posteriorly into the pharynx and superiorly between the developing palatal folds. The constellation of micrognathia, glossoposis, and U-shaped cleft of the soft palate is termed the *Pierre Robin sequence* (PRS). The crowding of the oropharyngeal space in this condition has been associated with OSA, failure to thrive, cor pulmonale, neurocognitive impairment, and death (13, 14). In 80% of cases, the Robin sequence occurs as part of a syndrome including Stickler, velocardiofacial, fetal alcohol, Nager, Treacher Collins, and hemifacial microsomia syndromes (15). Micrognathic infants have a more collapsible upper airway (16) and most require an intervention to sustain airway patency (17), although some can successfully compensate via neuromuscular activation (14, 18). The degree of airway obstruction in infants with the Robin sequence is variable, with some obstructing only during sleep, and others during both wakefulness and sleep.

Maxilla

Maxillary hypoplasia is characterized by anteroposterior and/or mediolateral narrowing that may be congenital or acquired. The syndromic craniosynostosis syndromes, including Apert, Crouzon, and Pfeiffer syndromes, are also characterized by comorbid skeletal anomalies including choanal atresia and septal deviation, resulting in further increases in upper airway resistance. Despite airway narrowing, many maxillary-deficient infants are capable of successful neuromuscular compensation initially. However, OSA may develop after 6 months of age coincident with the normal development of adenotonsillar hypertrophy or during upper respiratory infections (12). Overall, the prevalence of OSA with craniosynostosis in the first year of life is approximately 40%, with many additional cases developing later (19). The principal nongenetic determinant of maxillary growth is the route of breathing. Mouth breathing in infants results in a narrow maxilla, high-arched palate, and increased lower facial height. This craniofacial pattern has been termed the "long face syndrome" and is associated with OSA. Thus, nasal obstruction adversely affects maxillary growth and predisposes toward ensuing OSA. Infants with midfacial hypoplasia may develop life-threatening OSA in the first year of life (20). Corrective surgery in infancy should be considered in the setting of severe OSA, but if midfacial advancement cannot be performed or is delayed, then CPAP or tracheostomy is the preferred option.

Soft Tissues

Adenotonsillar hypertrophy may become an important contributor to OSA in infants after 6 months of age. Adenotonsillar enlargement is especially common after an upper respiratory infection, or associated with systemic disorders such as sickle cell disease

or glycogen storage disorders. Comorbid conditions may predispose toward worsening OSA in the setting of adenotonsillar hypertrophy, including hypotonia, craniofacial anomalies, and prematurity (21). Endoscopic evaluation of infants with gastroesophageal reflux (GERD) demonstrates swelling and erythema of the arytenoid cartilages, vocal cords, and subglottic region (22). GERD is increased in infants with OSA, although the relationship between the two is complex. Some studies have demonstrated a direct temporal relationship between OSA and GERD (23, 24), whereas others have not (25, 26). A large study in preterm infants, using both pH and intraluminal impedance, reported that less than 3% of apnea, bradycardia, or desaturations was preceded by GERD (27). Menon and colleagues reported a 14-fold increase in apnea frequency immediately after regurgitation, yet the majority of apneic events were not associated with GERD (24). The apparent discrepancy in the relationship between GERD and apnea may relate to patient selection. The temporal relationship between GERD and apnea is poor in infants evaluated for an apparent life-threatening event (ALTE) (26). Nevertheless, GERD may directly trigger an OSA in some infants through the laryngeal chemoreflex or result in upper airway swelling without a clear temporal association. Conversely, episodes of GERD frequently follow obstructive events, perhaps mediated by large negative intrathoracic pressure swings (26, 27). Apnea severity has been shown to improve after successful treatment of GERD in infants (23).

CONGENITAL AND ACQUIRED AIRWAY ABNORMALITIES

There are a multitude of airway anomalies that result in increased upper airway resistance and OSA in infants (*see* Table 1). The most common infant airway abnormalities are as follows:

1. Laryngomalacia refers to an inspiratory collapse of the epiglottis and arytenoid cartilages resulting in airway obstruction. Laryngomalacia is the most common cause of inspiratory stridor and OSA in infants. Comorbid airway lesions have been reported in 10–50% of patients, particularly tracheomalacia and subglottic stenosis (28). Laryngomalacia is associated with, and perhaps exacerbated by, gastroesophageal reflux, and will typically spontaneously improve over the first 12–18 months of life. However, approximately 20% of infants with laryngomalacia will have severe OSA, hypoxemia, or failure to thrive, and may require surgical therapy. Supraglottoplasty has been reported to reduce obstructive events, increase the total sleep time, and improve oxygen saturation (29, 30). Although infants usually improve after supraglottoplasty, considerable residual OSA may remain (29, 30), particularly with comorbid conditions including micrognathia, neuromuscular disease, tracheomalacia, or tonsillar hypertrophy (31, 32).
2. Choanal atresia is a congenital narrowing of the posterior nasal airway, which can present with considerable respiratory distress, including death. It is often associated with genetic conditions including CHARGE, Crouzon, and Treacher Collins syndromes. The obstruction may be classified as mixed membranous/bony (70%) or bony (30%) (33), and may be unilateral (45%) or bilateral (55%) (34). Bilateral choanal atresia presents at birth with airway obstruction, whereas unilateral choanal atresia presents later in infancy with nasal congestion and disturbed sleep. The diagnosis of choanal atresia is definitively established by computerized tomography and surgical treatment is highly effective.

3. Cleft palate may arise as part of a syndrome (70%) or occur as an isolated anomaly (30%) (35), and is associated with a smaller posterior airway space (36) and a high risk of OSA (37). The surgical closure of a cleft palate in infants with craniosynostosis (midfacial hypoplasia) may result in further airway narrowing and OSA. Even nonsyndromic clefts may also have a degree of maxillary hypoplasia. Children with repaired cleft palate have impaired anteroposterior growth of the maxilla that may predispose toward future OSA (38). Approximately 20% of children with a cleft palate will require pharyngoplasty or a pharyngeal flap to treat velopharyngeal insufficiency, which further increases the risk of OSA (39, 40). Cognitive impairments are frequently observed in children with cleft palate, and longstanding OSA may be an important contributing factor.
4. Subglottic stenosis is a narrowing of the laryngeal lumen at the level of the cricoid cartilage, which may be congenital or acquired. Congenital subglottic stenosis may be due to soft tissue hypertrophy or cartilaginous narrowing. Endoscopy reveals a subglottic diameter of less than 4 mm in a term infant. Infants typically present with biphasic stridor and varying degrees of respiratory distress. Most infants with mild disease will gradually improve as the larynx grows. Infants with gas exchange abnormalities, feeding difficulties, or OSA may require surgical repair or tracheostomy. Acquired subglottic stenosis occasionally arises after intubation in neonates, and appears to be exacerbated by prolonged intubation, infections, and GERD.

ONTOGENY OF AIRWAY AND RESPIRATORY PHYSIOLOGY

The infant upper airway is a highly compliant conduit in which a 2-cm H₂O change in luminal pressure results in a 50% reduction in cross-sectional area (41). This property results in rapid changes in the caliber of the airway contributing to ventilatory instability, and therefore obstructive cycling. Airway muscle activity modulates the cross-sectional area and the compliance of the airway. Although term and preterm infants show a brisk genioglossal EMG response to upper airway occlusion or increased resistance during sleep (42, 43), an immediate and sustained decline in minute ventilation is observed (11, 44). The mean airway closing pressure for infants at 2 months of age is -0.5 cm H₂O under complete paralysis during anesthesia (41) and is -0.7 ± 2 cm H₂O in postmortem studies (45). Thus, in the absence of muscle activity the viscoelastic airway closing pressure is close to atmospheric pressure, indicating a high risk for collapse. During the first year of life, the infant's airway becomes more stable, with a reduction in the passive closing pressure to -6 cm H₂O (41). During sleep, however, the closing pressure in infants is less than -25 cm H₂O, indicating the effectiveness of neuromuscular activation to sustain pharyngeal patency (46). Infants with neuromuscular weakness may have impaired motor control of upper airway dilators contributing to OSA.

Infants have a highly compliant rib cage resulting in paradoxical respirations, which may persist up to 3 years of age during REM sleep (47). Because the compliance of the infant lung is similar to that of an adult, the net result is a smaller relaxation lung volume. Breathing at such low lung volume results in increased work of breathing and a decreased pulmonary reserve of oxygen. Consequently, infants actively maintain an end-expiratory volume above the passively determined relaxation volume via expiratory laryngeal closure, postinspiratory diaphragmatic activity, and tachypnea. These mechanisms appear to be intact during non-rapid eye movement (NREM) sleep but

are attenuated or absent during REM sleep, resulting in lower lung volumes and a propensity toward oxygen desaturation with normal respiratory pauses (48). These mechanisms may be impaired in the setting of vocal cord dysfunction or diaphragmatic paralysis, and may lead to respiratory distress in infants. By 6 to 12 months of age, the chest wall compliance has decreased, and large improvements in pulmonary reserve can be expected.

ONTOGENY OF VENTILATORY CONTROL

The principal determinant of central respiratory drive and upper airway tone is the carbon dioxide (CO_2) level. During NREM sleep, the coefficient of variation of minute ventilation is highest in preterm infants (39%), compared with term infants (25%) and adults (14%) (49). Further, peripheral chemoreceptor function, as measured by a 100% oxygen challenge, demonstrates a much larger reduction in minute ventilation in infants (38%) compared with adults (6%), thus contributing to infant ventilatory instability (50). Peripheral chemoreceptor activity is also greater in infants experiencing periodic breathing (50). Both the hypoxemic and hypercapnic ventilator drives decrease during sleep and an apneic threshold level to CO_2 emerges that is not present during wakefulness. In infants, the CO_2 apneic threshold is approximately 1 mm Hg below eupneic breathing (51). By contrast, adults have a difference of 4 mm Hg between eupnea and the apneic threshold, leading to more stable ventilation. Thus, ventilatory instability, especially the opening and closing of the airway, may exacerbate obstructive cycling by causing oscillations in ventilation. Consequently, obstructive, mixed, and central apneas occur at the nadir of the ventilatory drive cycle at which pharyngeal dilator activity is at a minimum (52). Some of the variability in infant breathing patterns may also relate to the proportion of time spent in REM sleep, which is 60% at birth, and 30% at 1 year of age. Supplemental oxygen therapy stabilizes the breathing pattern in infants, reducing the amount of periodic breathing and obstructive apnea (53). However, supplemental oxygen may also eliminate the oxygen desaturation associated with obstructive events that are not primarily influenced by ventilatory control, thereby obscuring their identification but not their subtle sleep-disruptive effects.

ONTOGENY OF SLEEP ARCHITECTURE AND AROUSAL

Arousal constitutes a paroxysmal, transient intrusion of a state of heightened vigilance into sleep. Infant arousal is a stereotyped, hierarchical process beginning in the brainstem, with rostral spread as necessary, to sustain homeostasis in response to a respiratory or nonrespiratory stimulus. A similar arousal sequence is observed in response to hypercapnia, airway occlusion, or tactile stimulation (54). By contrast, hypoxemia is a weak stimulus for arousal in infants (55). Minor increases in upper airway resistance induce arousal responses localized to the brainstem including changes in heart rate and blood pressure. The next level of responses includes augmented breaths and startles, which also derive from the brainstem (56). Sighs are important to redistribute surfactant and maintain ventilation-perfusion matching. A startle results in head movement that might facilitate repositioning to unblock the airway. Last, the infant may engage in a robust arousal characterized by thrashing movements that may progress to eye opening, awakening, and crying. Thus, the infant uses progressively increasing nonspecific movements as a mechanism to reopen the airway. The underlying sequence is the same in REM and NREM sleep, although cortical arousals are more common in REM sleep (57). Arousal in infants also results in atypical EEG arousal including high-voltage delta activity and a voltage attenuation pattern. Although arousals alleviate the gas exchange abnormalities and

normalize respiratory effort, they may do so with the untoward sequelae of sleep fragmentation. Thus, arousal must be viewed as both an essential protective mechanism and as an epiphenomenon adversely affecting sleep quality. Moreover, arousal may lead to ventilatory overshoot that may potentiate obstructive cycling.

Wulbrand and colleagues studied arousal in normal infants in response to airway occlusion, and observed that (1) all challenges resulted in a startle characterized by neck extension, EMG activation, and heart rate acceleration; (2) an augmented breath was consistently present; and (3) only 45% of occlusions demonstrated cortical arousal, although most were less than 3 seconds in duration (58). However, this sequence of movements may be ineffective at uncovering the face or result in a more obstructed facial position (56). In response to spontaneous airway closure during sleep, only 18% of NREM and 12% of REM sleep obstructions terminate with EEG arousals (59). Even in the absence of cortical arousal, startles and augmented breaths have been observed to temporarily interrupt spindle activity, suggesting involvement of thalamic neurons (60). Also, augmented breaths in infants are associated with marked increases in pharyngeal dilator activity (18). Thus, the preponderance of data supports the concept that airway opening mechanisms in infants are primarily a function of brainstem reflexes, independent of cortical arousal. Sleep deprivation is associated with an increased arousal threshold that may impair ventilatory control mechanisms, resulting in increased obstructive sleep apnea (61). Infection seems to increase the arousal threshold as well as upper airway resistance, thus augmenting OSA in infants (62, 63).

NORMATIVE DATA

Accurate interpretation of the infant polysomnogram requires a thorough understanding of age-specific normative data. Breathing patterns in infancy are dependent on postconceptual age, recording techniques (thermistor vs. nasal pressure), length of observation, ambulatory versus laboratory-based studies, oximetry averaging interval, and event definitions. We focus on respiratory patterns identified during comprehensive overnight polysomnography. Rebuffat and colleagues demonstrated little night-to-night variability in sleep state or apneas in overnight polysomnograms from 19 term infants on two or three successive nights (64). REM sleep accounts for 50–60% of the total sleep time in term infants, but may comprise 90% in premature infants born at 30–32 weeks of gestation. At 1 year, REM sleep accounts for 30% of the total sleep time. Comparison between premature infants who reach a postconceptual age of 40 weeks and term infants reveals similar breathing patterns. The median respiratory rate in term infants at birth during sleep is 40 breaths/minute (10–90th percentile is 32–66 breaths/min); this decreases to 35 breaths/minute (10–90th percentile is 24–45 breaths/min) by 3 months of age and to 23 breaths/minute (10–90th percentile is 20–28 breaths/min) at 1 year old (65). In a population of infants referred for evaluation of apnea, there was no difference in the incidence of OSA between the prone and supine positions (66, 67). Normative polysomnographic data for infants are presented in Table 2. REM sleep is readily identifiable in term infants and therefore infant sleep may be scored as REM versus NREM (68). The median baseline oxygen saturation as determined by pulse oximetry (SpO_2) during sleep in a term infant at birth is approximately 98% (10th–90th percentiles are 95–100%) and the median low is 83% (10th–90th percentiles are 78–87%) (69). Brief decreases in SpO_2 to less than 90%, totaling approximately 6 seconds/hour, are observed in most term infants at birth during periodic breathing, after normal respiratory pauses, and during REM sleep (69). Episodes of

TABLE 2. POLYSOMNOGRAPHIC DATA IN NORMAL TERM INFANTS AND CHILDREN

	0–2 mo	5–6 mo	12 mo	3–5 yr	10–17 yr
NREM sleep, % TST	40*	65	70	77	83
REM sleep, % TST	60	35	30	23	17
EEG arousal index, per h TST	13.1–19 ± 4.4	6 ± 2.3	6–7 ± 2	6–7 ± 2–3	6–7 ± 2–3
Obstructive apnea, per h TST	0.6–2	0.4–1	<0.5	<0.1	<0.1
Respiratory rate, breaths/min	40 ± 6	29 ± 5	24 ± 2	20 ± 1	18 ± 1

Definition of abbreviations: EEG = electroencephalogram; TST = total sleep time; NREM = non-rapid eye movement.

Data are from References 8, 57, 65, and 168–175; and the authors' experience.

*Includes indeterminate sleep.

desaturation are minimal after 6 months of age, coincident with the increase in lung volume (*see* the preceding discussion) (70).

The optimal definition of an obstructive event, particularly hypopneas and respiratory effort-related arousals, has not been established in infants. Most studies have reported only obstructive and mixed apneas, using thermistor-based studies. Complicating the situation is that airway closure has been observed in 47% of central apneas in preterm infants (71). Because of the rapid respiratory rates in infants, an obstructive event is usually defined as lasting for two or more breaths. Obstructive apnea or mixed apnea appears to be more common in premature infants and decreases in frequency over the first year of life. Guilleminault and colleagues reported that term infants have an obstructive apnea rate of 0.6/hour at 3 weeks, 1.1/hour at 6 weeks, 0.4/hour at 3 months, and 0.2/hour at 6 months (72). Similarly, Hoppenbrouwers and colleagues reported an obstructive apnea rate of 0.7/hour at 1 month, 0.6/hour at 3 months, and 0.2/hour at 6 months (73). In preterm infants, an obstructive apnea rate of 1/hour was observed at a postconceptual age (PCA) of 40 weeks, 0.7/hour at a PCA of 44 weeks, and 0.5/hour at a PCA of 52 weeks (73). Obstructive events are associated with a much greater decline in oxygenation and heart rate compared with central apneas of equal lengths of time (74). Potential mechanisms mediating the enhanced hypoxemia during obstructive apneas include decreases in lung volume, increased metabolic work of breathing, and/or a decrease in cardiac output. In the largest cross-sectional study to date, Kahn and colleagues studied 2,073 infants between 25 and 43 weeks gestational age, at 1–51 weeks of age (75). Overall in REM sleep, infants had an obstructive apnea rate of 0.6/hour, lasting a mean of 5.2 seconds (8 s for mixed apneas). In NREM sleep, an obstructive apnea rate of 0.1/hour was observed.

PATHOPHYSIOLOGY OF OBSTRUCTIVE PATTERNS IN INFANCY

OSA is characterized by increased upper airway resistance during sleep. The airway narrowing may be due to craniofacial abnormalities, soft tissue enlargement, and/or neuromotor dysregulation (*see* Table 1). Airway collapse occurs when the airway wall pressure exceeds the luminal pressure. In infants without laryngeal abnormalities, the site of airway obstruction has been measured with multiple pressure transducers and found to be retropalatal in 52% and retroglossal in 48% (76). Neck position appears to be an important determinant of airway collapsibility in infants. Neck flexion of 15–30 degrees increases collapsibility by 4–5 cm H₂O, whereas neck extension decreases collapsibility by 3–4 cm H₂O (45). These changes are sufficient to be an important determinant of airway patency during tidal breathing. By contrast, neck rotation appears to have little influence on airway collapsibility or respiratory pattern in most infants (45, 77).

Airway closure in infants may occur as a passive or active process producing different polysomnographic patterns that are predicated on the predominant underlying pathophysiology:

1. **Anatomical:** Infants with severe anatomical abnormalities such as micrognathia or nasal obstruction have increased upper airway resistance accompanied by marked increases in respiratory effort, and therefore negative luminal pressure. These infants typically manifest loud snoring with marked labored breathing and complete obstructions often terminating with an arousal. Despite a brisk genioglossal EMG response to upper airway occlusion or increased resistance during sleep (42, 43) infants have an immediate and sustained decline in minute ventilation (11, 44). Infants with OSA have a decreased activation of the major upper airway dilator muscle compared with nonapneic control subjects (43) in response to airway occlusion, potentially impairing the ability to respond to airway closure (43). During spontaneous obstructions in term infants, decreased respiratory effort has been measured at the start of an obstructive event, followed by a gradual increase in effort above baseline by the third breath (76). By contrast, preterm infants have decreased respiratory effort throughout a spontaneous obstructive event (78). Thus, term infants frequently demonstrate a robust neuromuscular reflex activation of the upper airway during obstruction, which may be absent in preterm infants.
2. **Ventilatory control:** Periodic breathing is common in the first several months of life and is characterized by respiratory pauses of more than 3 seconds, separated by less than 20 seconds of crescendo–decrescendo ventilation. A mixed apnea may occur at the nadir of these ventilatory control oscillations in CO₂ levels, when muscle activity is at a minimum. Our preference is to score this as periodic breathing, and to report the obstruction observed at the nadir. Snoring may be absent and little labored breathing is apparent. These events may be associated with significant oxygen desaturation and arousal may be present during the ventilator phase of the cycle. Arousal may contribute to the ventilatory overshoot that promotes ensuing obstructive cycling. Similarly, upper airway closure has been reported in more than 50% of central apneas in premature infants (79).
3. **Laryngeal chemoreflex:** Airway closure may occur as an active process resulting in stimulation of the laryngeal afferents, termed the *laryngeal chemoreflex*. This important airway defense mechanism aims to avert laryngeal penetration of airway fluid. Apneic events induced in this manner typically feature an arousal at the outset and a series of swallows and ineffectual breaths during which the larynx has been actively closed. The polysomnographic pattern includes central apnea, swallowing, obstructive apnea, arousal, and bradycardia (80, 81). Clinically, approximately 22–26% of apneas are associated with swallowing, which may be evident by increases in the chin EMG (82). However, overall only 4% of swallows were associated with apnea (82). Of the apneas coinciding with swallowing, 25% of swallows preceded the apnea, and 75% occurred during the apnea (82). Arousals were

associated with swallows in 34% of instances, but swallows were rarely associated with arousals. Thus, once an apnea or arousal occurs, swallowing is common, but swallowing does not generally induce apnea or arousal.

CLINICAL FEATURES

Snoring is observed in most infants diagnosed with OSA (83). However, snoring is also prevalent in the general population, occurring in 11.8% of infants at least 2 days/week, and in 5.3% at least 3 days/week (84). Risk factors for snoring in infancy include maternal smoking and being overweight (85). Less than 10% of snoring infants have polysomnographic evidence of OSA. Infant OSA is more frequently observed with prematurity (86), prenatal smoking (87), bronchopulmonary dysplasia (88), males (89), obesity (90), and in younger babies. Infants with chronic lung disease have an increased incidence of OSA and unsuspected sleep-associated hypoxemia (91), which may also be associated with poor growth (92). Infants with Prader-Willi syndrome and who are receiving growth hormone have been observed to develop OSA during upper respiratory infections (63, 93). Many infants with ALTE presentations have documented OSA (72) or eventually develop OSA (94). In addition, infants with OSA more often have a positive family history of OSA and craniofacial risk factors for OSA (95). The obstructive sleep-disordered breathing indices of infants with OSA appear to lessen over the first 6–12 months of life (96, 97).

There is considerable overlap in symptomatology between infants with and without OSA. A population-based study reported snoring or noisy breathing in 22–26% of normal infants, compared with 26–44% of infants with OSA (98). The diagnosis of OSA has been reported to be delayed in infants because of a lack of symptomatology and a normal physical examination (99). Infants referred to a subspecialty clinic with OSA most commonly had snoring, witnessed apnea, and recurrent respiratory infections with occasional failure to thrive and developmental delay (100). Infants with OSA may also experience labored breathing, frequent movements, awakenings, mouth breathing, profuse sweating during sleep, breath-holding spells, and dysphagia (83, 101). An experimental protocol whereby normal infants were deprived of a single morning nap resulted in an increased obstructive event index from a baseline of 0.4/hour to 6.2/hour (102). It is postulated that sleep deprivation may act by adversely affecting ventilatory control mechanisms, arousal threshold, and airway neuromuscular tone (61). Sleep deprivation is also a risk factor for sudden infant death syndrome (SIDS) and may arise as the result of a viral infection or OSA. The long-term consequences of brief obstructive apneas in otherwise well infants have not been established. However, even nonapneic infants with snoring-induced arousals may have lower impaired developmental performance testing (103).

The preponderance of studies have reported a higher incidence of obstructive events in otherwise normal infants during REM sleep (66, 73, 74, 82), but some have not (104). REM sleep is associated with hypotonia of the chest wall and upper airway muscles, lower lung volumes, paroxysmal reductions in pharyngeal tone, and increased respiratory variability. Also, compensation for increased nasal resistance is less robust during REM sleep (11). Thus, both obstructive events and hypoxemia preferentially occur during REM sleep. Whereas older children with OSA have a similar proportion of REM sleep compared with control subjects (105), two studies of infants with OSA have reported a reduction in REM sleep (97, 106), with subsequent increase after treatment (107). CPAP is an effective therapy for infants with OSA (108, 109), although noncompliance

was reported in 25% of patients (107). CPAP has been hypothesized to mechanically splint open the airway (110), increase end-expiratory lung volume (111), and reduce thoracoabdominal asynchrony (111) in infants. McNamara and Sullivan reported that infants with OSA generally required between 4 and 6 cm H₂O for optimal treatment, and that CPAP could be used long-term in infants with craniofacial abnormalities (107). CPAP therapy for OSA improved growth velocities in infants with failure to thrive.

Infants who subsequently die of SIDS have slightly more obstructive events than control children (112). However, obstructive events were nevertheless rare in future SIDS victims at 0.5 event/hour (range, 0–3.8/h) (112). In addition, the few obstructive events were of the same length, with a similar amount of oxygen desaturation as in control infants (113). By contrast, the relative risk of OSA in infants has been reported to increase in subsequent siblings of SIDS victims, after ALTEs, and with a family history of adult OSA (96, 114, 115). Mild dysmorphism predisposing toward OSA may be observed in infants presenting with ALTEs including micrognathia/retrognathia (115, 116) and elongated uvula (115). Thoracoabdominal asynchrony, suggestive of increased respiratory effort, has also been reported in infants with ALTE (117). Infants that develop OSA are more likely to have a family history of OSA and nasal allergies, indicating that immune function and craniofacial traits may be risk factors for OSA early in life (95).

DIAGNOSIS

A clinical history of symptoms and predisposing risk factors for sleep-disordered breathing is the cornerstone for identifying infants at risk for OSA. Nevertheless, there is considerable overlap in the incidence of symptoms of sleep-disordered breathing, including snoring, in infants with and without OSA (98). In addition, infants with OSA typically have a normal physical examination during wakefulness. Overall, the clinical history and physical examination alone are a poor predictor of objectively measured airway obstruction. Consequently, polysomnography (PSG) represents a necessary diagnostic modality toward establishing the existence and severity of OSA in infants (118). A PSG is indicated whenever the clinical evaluation is suggestive of sleep-disordered breathing, particularly in infants with risk factors for OSA including craniofacial abnormalities, prematurity, obesity, neurological disorders, and genetic conditions. Of considerable importance is the observation that many infants with micrognathia and OSA do not snore, thus necessitating routine polysomnography (119, 120). A follow-up polysomnogram after treatment is recommended in infants with moderate to severe OSA, craniofacial abnormalities, or neurological disorders (118). Infants presenting with an ALTE may also benefit from polysomnography if there are specific concerns regarding upper airway obstruction, or if there is documentation of hypoxemia during sleep (118). Last, polysomnography should also be considered in infants with laryngomalacia associated with a clinical history of respiratory distress during wakefulness or sleep.

Infants with OSA should generally be evaluated by fiberoptic nasopharyngoscopy to ascertain nasal patency, septal position, adenoidal volume, pharyngeal patency, laryngeal stability, mucosal swelling, and vocal cord function. Also, upper airway endoscopy under sedation can document dynamic closure of the pharynx or larynx in infants with normal tone and no obvious anatomical narrowing (121). Although laryngomalacia will frequently be evident on nasopharyngoscopy, infants with moderate-severe OSA or respiratory distress should also subsequently undergo direct laryngoscopy under anesthesia to identify comorbid airway lesions.

Nasopharyngoscopy and direct laryngoscopy should also be considered in infants with PRS to evaluate for nasal anomalies and subglottic stenosis (122).

There is an individual trait susceptibility to the neurocognitive, cardiovascular, and neurocognitive consequences of OSA. Thus, there is no strict threshold level of OSA severity that mandates treatment in all infants. Our approach is to consider the severity of the OSA in relation to the therapeutic options, the natural history of the underlying condition producing the OSA, and the clinical symptomatology. A step-wise approach to therapy is recommended, starting with the most benign interventions such as prone positioning, oxygen, or antireflux therapy, progressing to nasopharyngeal tubes or CPAP, and ultimately resorting to surgical interventions. As a guideline, an infant found to have an apnea-hypopnea index (AHI) greater than 2/hour should alert physicians as to the probable presence of significant OSA. A few obstructive events during sleep (<1 event per hour of total sleep time [TST]) are commonly observed in otherwise normal infants and have not been clearly associated with adverse outcomes. Nevertheless, the observation that snoring alone in infants, without apnea, may lead to adverse neurobehavioral sequelae indicates the presence of subtle disruptions in sleep homeostasis that may pose a risk to susceptible infants. As a guideline, OSA is typically characterized as mild (AHI, between 1 and 5/h; $SpO_2 < 90\%$ for 2–5% of TST), moderate (AHI, 5–10/h; $SpO_2 < 90\%$ for 5–10% of the night), and severe (AHI, >10 /h; $SpO_2 < 90\%$ for $>10\%$ of the night). An elevated arousal index should typically raise the category of severity.

TREATMENT APPROACH

Conditions likely to resolve spontaneously, including reflux-induced airway swelling, nonsyndromic micrognathia, and laryngomalacia, may reasonably be managed by temporizing interventions, unless the obstruction is too severe. Infants who have profound oxygen desaturation, moderate–severe OSA, failure to thrive, or developmental delay must receive more aggressive therapy. The decision to start CPAP therapy in infant requires clear evidence that the OSA is likely to result in adverse sequelae. CPAP is often poorly tolerated by the infant, and is thus associated with considerable sleep disruption. Realistically, desensitization to CPAP may take several weeks, during which a caregiver will need to be present to reposition the mask and comfort the infant. In addition to the baseline level of OSA present, clinicians must be cognizant of the adverse effects that intercurrent viral infections may have on sleep-disordered breathing. Infants must have sufficient reserve in their upper airway function to tolerate expected virus-induced increases in upper airway resistance. Last, the presence of comorbidities influences the choice of therapy for OSA. In particular, infants with neuromuscular disorders may have poor upper airway compensatory mechanisms.

The approach to a micrognathic infant is based on the likely natural history of the condition (123). Nonsyndromic micrognathia arises from abnormal positioning *in utero*, posing a physical impediment toward development. After birth, the deformational forces are relieved, and mandibular growth as well as neuromotor maturation occur. Although the mean mandibular length growth velocity is normal, catch-up growth does not occur, and there remains a relatively small mandibular height (124). Nevertheless, temporizing treatments are generally sufficient, including prone positioning (125) or nasopharyngeal stenting (126) for several months. By contrast, infants with syndromic micrognathia often have a genetic growth disturbance, and are not expected to have normal postnatal mandibular growth; in addition, their upper airway motor control may be impaired. Airway obstruction in infants with syndromic micrognathia may worsen in the first year

of life and long-term follow-up studies indicate that 65% have chronic snoring or OSA (13). These infants may require mandibular distraction (127), CPAP (128), or tracheostomy. After mandibular distraction, most infants have a resolution of their OSA within a few weeks, and long-term follow-up suggests that 80% of these infants remain free of OSA (129).

Medical Therapy

Infants with the PRS sequence may experience less airway obstruction in the prone position, but this therapy alone is adequate only in infants with mild obstruction. Infants with PRS should undergo nasopharyngoscopy and bronchoscopy to determine the site of obstruction and to identify any comorbid airway abnormalities. Although prone positioning has been associated with a two-fold increase in SIDS, the overall incidence of SIDS in prone-sleeping infants remains less than 2 per 1000 infants. In infants with PRS sequence, the improvement in OSA observed in the prone position may result in a favorable risk-to-benefit ratio for this intervention. We recommend continuous pulse oximetry monitoring of all infants placed prone. Positional therapy was successful by clinical report in improving airway obstruction in 72% of infants with nonsyndromic PRS and 50% of infants with syndromic PRS (120). However, the observation that micrognathic infants with OSA may be relatively silent during apnea mandates that comprehensive polysomnography be used to verify improvement (119, 120). Approximately one-third of infants with PRS who fail to respond sufficiently to positional therapy will respond to nasopharyngeal airway intubation (120). A standard 3.0- or 3.5-sized endotracheal tube placed transnasally to the level of the hypopharynx is used to stent open the airway, thus alleviating OSA. Most infants respond dramatically to the nasopharyngeal tube but they are unable to feed, and the tube must be replaced every 4–6 weeks. Parhizkar and colleagues reported that 75% (26 of 35) of infants with micrognathia treated by nasopharyngeal airway placement did not require any further airway intervention, although objective testing was not performed (126).

CPAP will successfully reverse obstructive sleep-disordered breathing in most infants, although compliance is often poor. There are commercially available nasal masks suitable for an infant and few, minor side effects have been reported, including eye irritation and breakdown of the skin on the face. Our practice is to initiate CPAP in infants in a monitored hospital setting to facilitate acceptance of the mask, followed by a CPAP titration study to ensure therapeutic efficacy. A repeat CPAP titration study is typically performed in infants after 2–6 months of therapy, depending on the natural history of the obstruction, intercurrent treatments, and/or the presence of signs or symptoms of OSA. Infants with OSA may have clinical symptoms or endoscopic signs of gastroesophageal reflux. The natural history of GERD in infants is spontaneous resolution by 12–18 months of age. Management with small, frequent, thickened feeds is often sufficient. Consideration for an evaluation for anatomical abnormalities, dysmotility disorders, or allergic conditions may be indicated. Careful follow-up of infants with OSA is required to rapidly identify residual disease posttherapy or recurrent disease later in life.

Surgical Therapy

Adenotonsillectomy (T&A) or adenoidectomy is effective therapy for OSA in infants with adenotonsillar hypertrophy (83, 130), although residual OSA is common (130). T&A for OSA in infants has been reported to improve growth and development (83, 131). However, infants with OSA undergoing T&A have more postoperative respiratory and airway complications than older children (132). Also, after T&A, 65% of children less than

3 years old with OSA have at least moderate residual OSA (132) compared with 29% of older children (133). Infants should be monitored carefully, in the hospital, after T&A for obstruction and hypoxemia that may require CPAP or reintubation (21, 134).

Surgical management of laryngomalacia in infants with OSA has evolved away from tracheotomy in favor of supraglottoplasty, using endoscopic techniques, resulting in reduced morbidity and resolution of OSA in the majority of infants (29, 30). A supraglottoplasty includes incising the aryepiglottic folds to release the epiglottis, removing redundant soft tissue overriding the accessory cartilages, and removing the lateral edges of the epiglottis. Before performing the endoscopic operative procedure the airway must be fully evaluated by direct laryngoscopy and bronchoscopy to determine the presence of any synchronous airway lesions. Complications are rare after supraglottoplasty and the infant usually requires 1–2 days of hospitalization.

Infants born with syndromic micrognathia often present with severe OSA that may persist long term because of poor mandibular growth, and are more likely to benefit from mandibular distraction. The choice and urgency of therapy are predicated on the severity of the airway obstruction, the presence of obstruction when awake, and the adequacy of feeding. These infants often receive temporizing treatments, including prone positioning, oxygen, CPAP, or a nasopharyngeal tube. These therapies are frequently ineffective or are too poorly tolerated to be used long term. With CPAP, a considerable effort is made at providing a properly fitting mask and to facilitate acceptance of this mode of therapy. Cheng and colleagues reported that 6 of 20 infants with the PRS failed a trial of CPAP (135). Infants with PRS and OSA who are not responsive to medical management are evaluated for surgical intervention, including lip–tongue adhesion, mandibular distraction, and tracheostomy. Our experience over the last decade supports the use of mandibular distraction as the first-line surgical treatment.

Lip–tongue adhesion (LTA) consists of a surgical fixation between the mucosa and muscles of the lip and tongue. LTA is a relative simple operation with rare serious long-term complications. Bijnen and colleagues reported that LTA resulted in clinical improvement in OSA in 60% of infants with isolated tongue-base obstruction (136). Sedaghat and colleagues documented at least partial polysomnographic improvement after LTA in eight infants with PRS (137). Preoperatively, seven of eight infants had severe OSA, and postoperatively, one infant had resolution of OSA, two had mild OSA, and two had moderate OSA. Thus, residual moderate to severe OSA was present in five of eight infants. Similarly, Denny and colleagues performed LTA in 11 infants with PRS (7 syndromic) and reported that 10 of the infants required an additional airway intervention (138).

Mandibular distraction osteogenesis (MDO) involves bilateral osteotomies of the mandibular rami, and the placement of a distraction apparatus bilaterally. The surgery requires approximately 3 hours, results in less than 30 ml of blood loss, and infants are generally extubated within 3–6 days (139). The device is extended daily 1–2 mm for 3 weeks, left in place for 3 months, and then removed. The goal of distraction is produce a 23- to 30-mm distraction resulting in a slight overcorrection with a class III malocclusion (135). Mandibular distraction has been reported to alleviate sleep-disordered breathing in micrognathic infants, as well as to improve feeding and growth (140, 141). The preponderance of studies have reported both short- and long-term near-normalization of OSA after MDO (139, 142). However, Cheng and colleagues reported a series of PRS infants with comorbid airway lesions including laryngomalacia, choanal atresia, tracheal stenosis, and epiglottal abnormalities who had moderate or severe residual OSA after MDO and LTA

(135). In infants with syndromic micrognathia, nasopharyngoscopy and/or imaging studies are helpful in clearly determining the site of obstruction and to identify comorbid airway abnormalities. Infants with Stickler syndrome typically have isolated micrognathia, whereas infants with Treacher Collins syndrome or Nager syndrome commonly have secondary sites of obstruction. MDO is reserved for infants in whom the tongue has been documented to abut the posterior pharyngeal wall, either directly or with the soft palate interposed. Infants with evidence of obstruction other than the posterior tongue may not benefit from MDO, and tracheostomy should be considered (139). After MDO, infants with PRS may generally have successful closure of their cleft palate (139). Complications of MDO, rarely reported, include facial nerve injuries, facial scarring, disruption of tooth buds, and temporomandibular joint dysfunction.

Infants with craniosynostosis (midfacial hypoplasia) often experience relief of OSA after placement of a nasopharyngeal tube (143, 144). However, one large series reported that 48% of patients with syndromic craniosynostosis required tracheotomy for airway obstruction (145). Infants with craniosynostosis usually have OSA due to naso- and oropharyngeal crowding that is multifactorial in nature. Several surgical options are available depending on the age of the child and the site of obstruction. T&A is helpful in older infants and children with craniosynostosis, although residual OSA is frequently present (146). Single-stage midfacial advancement is associated with considerable morbidity and has variable success in relieving OSA in children with craniosynostosis (147, 148). Gradual frontofacial distraction may provide greater advancement and more resolution of OSA (149). Often multiple surgeries are required and a tracheostomy and CPAP should be discussed and considered.

Tracheostomy placement in infants with craniofacial abnormalities is generally reserved for those with multiple sites of obstruction. The mean duration of tracheostomy placement in infants with OSA is 17 months in nonsyndromic children with PRS, and 32 months in syndromic children with PRS (120). Most infants undergoing tracheostomy will have a resolution of their OSA after mandibular growth during this interval (120). Tracheostomy may also be considered in an infant with OSA who is difficult to intubate and is likely to require multiple future surgeries. Tracheostomy in infants is associated with considerable morbidity including infections, tracheal stenosis, granulomas, bleeding, fistulas, tracheomalacia, and accidental decannulation (150, 151).

CONCLUSIONS

OSA in infants may arise from diverse airway abnormalities extending from the nose to the larynx. Establishing the specific cause of airway collapsibility is critical to selecting the optimal therapy. There are many challenges and unanswered questions regarding infant OSA: (1) The current technology for identifying obstructive events is often poorly tolerated and not widely available; (2) infants frequently lack frank EEG arousals associated with obstructive events and currently available tools for measuring autonomic arousals are highly variable; (3) little is known about the threshold level of obstruction that warrants intervention or long-term consequences of intermittent hypoxemia, sleep fragmentation, and increased respiratory effort; (4) the various craniofacial surgical techniques require better validation with polysomnography and long-term outcomes; and (5) longitudinal studies are needed to establish the relationship between OSA in infancy, childhood, and adulthood.

Author disclosures are available with the text of this article at www.atsjournals.org.

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