Chapter 11
Sleep-Disordered Breathing (SDB) in Pediatric Populations

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Introduction

When evaluating sleep-disordered breathing (SDB) in children, the sleep medicine specialist will see a broad range of respiratory problems beyond collapse of the upper airway. In addition to obstructive sleep apnea (OSA), the specialist should be prepared to evaluate control of breathing disorders, hypoventilation due to neuromuscular or thoracic cage disorders, and worsening sleep-related gas-exchange associated with chronic pulmonary conditions. The age spectrum will include infants to young adults with intellectual and other disabilities. Many referred children will have other comorbidities associated with increased risk of SDB such as obesity, genetic or craniofacial disorders, central nervous system (CNS) disorders,

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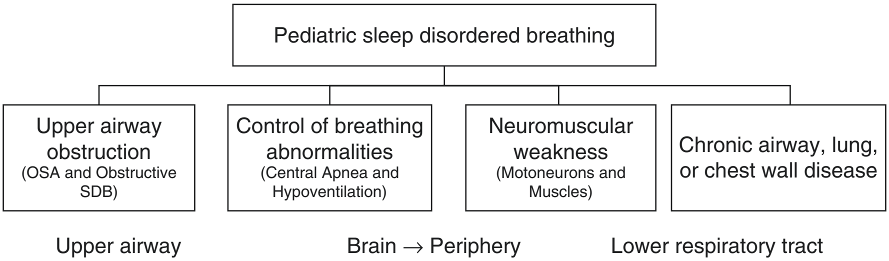

Fig. 11.1 Overview of pediatric sleep-disordered breathing

or neuromuscular disorders. Figure 11.1 presents a useful framework for thinking about the SDB in children in terms of understanding symptoms, signs, comorbidities, Polysomnography (PSG) findings, and planning a diagnosis and/or management approach.

This chapter provides summaries of the differences between pediatric and adult presentation of OSA, obstructive SDB in children, distinctive patient groups who are at high risk for SDB and respiratory-related hypoventilation and commonly referred for SDB evaluation, unique features of SDB in the first year of life, control of breathing disorders (central hypoventilation and central sleep apnea), and the basics of accommodating and evaluating children in sleep laboratory. More comprehensive references are listed for many topics.

Obstructive Sleep Apnea and Obstructive SDB in Children and Teens [1–4]

OSA is characterized by repeated episodes of partial upper airway obstruction and/or intermittent complete obstruction associated with disruption of gas exchange and sleep patterns. Anatomic and neuromotor problems contribute to its pathophysiology. The prevalence of OSA in healthy children is 1–5% but can exceed 50% in children with certain medical conditions (e.g., Down's syndrome, neuromuscular diseases, and craniofacial disorders). OSA has two age peaks in childhood. The first peak is in early childhood from ages 2–6 years, coinciding with normal lymphoid hyperplasia of tonsils and adenoids that surround the upper airway. The second peak appears after puberty, coinciding with weight gain and/or obesity. Table 11.1 summarizes risk factors for OSA in children.

Habitual snoring, prevalence 10%, is often the key presenting symptom, but not all snoring children have OSA. Table 11.2 lists symptoms and signs typically seen in children with OSA [1].

Clinical assessment does not reliably predict the presence or severity of OSA in children, but history and physical examination aids in risk assessment for OSA. In a large randomized controlled study of adenotonsillectomy in school-aged children

Table 11.1 Risk factors for obstructive OSA

Adenotonsillar hypertrophy
Comorbid conditions (obesity, craniofacial, neuromuscular, genetic)
Airway inflammation (nasal allergies, asthma)
Positive family history (two- to four-fold ↑ risk)
African American heritage (two- to four-fold ↑ risk)
Perinatal influences (prematurity, three-fold ↑ risk)
Prior adenotonsillectomy (unmasks anatomic and functional influences)
Socio-demographic (environmental tobacco smoke, neighborhood disadvantage, sleep deprivation)

Table 11.2 Symptoms and signs of OSA in children

History	Physical exam
Frequent snoring (≥3 nights/week)	Underweight or overweight
Labored breathing during sleep	Tonsillar hypertrophy
Gasping or snorting	Adenoidal facies or open mouth posture
Sleep enuresis (especially secondary)	Micro- or retrognathia
Sleeps sitting up or with neck hyperextended	High-arched palate
Cyanosis during sleep	Pectus deformity
Morning headaches	Hypertension
Daytime sleepiness	
Attention, behavior, or learning problems	

in which all participants had snoring, adenotonsillar hypertrophy, a standardized clinical history, and physical examination by pediatric ENT specialists, clinical parameters explained only 3% of the variance in the AHI [5, 6].

Laboratory-based PSG plays an important role in the diagnosis of OSA in children [1, 2, 7–12]. Although home-based sleep apnea testing (HSAT) is widely used in adults to diagnosis OSA in adult patients with high pretest probability of OSA, its use in children has been much more limited, reflecting concerns about safety feasibility, and reliability of collecting multiple respiratory signals in this population. Home sleep apnea testing (HSAT) devices are currently not recommended for use in children, but further research is needed to validate these approaches in children. More references on this topic are supplied later in the chapter.

Untreated OSA is associated with adverse consequences (attentional, behavioral, or learning problems; reduced quality of life, impaired growth, hypertension/cardiovascular stress, metabolic alterations and systemic inflammation, increased healthcare costs). In healthy children, adenotonsillar hypertrophy is the commonest cause of OSA and adenotonsillectomy is the first line of treatment, but success rates decrease significantly in children with underlying comorbidities. In a large randomized controlled trial of adenotonsillectomy in school-aged children with adenotonsillar hypertrophy and mild to moderate OSA, surgical treatment improved OSA symptoms, quality of life, PSG findings, behavior, and sleepiness [5, 13–15].

Patients should be reevaluated postoperatively for residual signs and symptoms to determine whether further treatment is required [9]. In otherwise healthy children, risk factors for persistence of OSA post-surgery includes obesity, African-American race/ethnicity, and higher obstructive apnea hypopnea indices [5]. In children with complex chronic conditions, residual SDB is common (30–60%) and anatomic and neuromotor problems are major contributors, so other surgical procedures and nonsurgical management may be needed [16].

Most children who do not respond to adenotonsillectomy or who are not candidates for adenotonsillectomy can be managed with PAP therapy [17, 18], but like adults, adherence is a challenge. Intranasal corticosteroids are an option for children with mild postoperative OSA or those who have not undergone adenotonsillectomy. Watchful waiting with supportive care may be appropriate for mild-moderate OSA [5]. Weight management and other lifestyle changes (exercise, sufficient and regular sleep) are recommended for patients who are overweight or obese. Novel dental or orthodontic treatments (e.g., rapid maxillary expansion, oral appliance to advance the mandible) may have a role in selected patients but more studies are needed to develop guidelines for this treatment of pediatric OSA. Positioning therapy may have a role in some selected patients.

Differences Between OSA Presentation Between Children and Adults

The clinical presentation and management of OSA differs between children and adults, but preteens and teens often present with a more adult-like picture (Table 11.3).

In children, adenotonsillar hypertrophy is the biggest risk factor for OSA, while obesity begins to play a stronger role in adolescence. There is no gender

Table 11.3 Comparison of OSA presentation in a child, adult, or obese child/teen

	Child	Adult	Obese child/teen
Gender	M = F	M>> > F	M> > F
Peak age	2–8 years	Mid-life	Preteen/Teen
Obesity	+	++++	++++
Craniofacial, genetic, or neuromuscular disorders	+++	+	++
Chief complaint for seeking medical attention	Snore Behavior/learning	Sleepiness	Snore, sleepiness Behavior/learning
Arousal	±	++++	+ to ++++
Respiratory pattern	Obstructive hypopneas ± hypoventilation	OSA	Obstructive hypoventilation to frank OSA
Treatment role for adenotonsillectomy	Common	Rare	Yes, but ↑ likelihood of residual OSA after surgery

Table 11.4 Comparison of OSA severity by obstructive AHI in pediatric and adult patients

	Pediatric	Adult
Mild	1–4.99	5–14.99
Moderate	5–9.99	15–29.99
Severe	≥10	≥30

predisposition in prepubertal children, but a male predominance appears in puberty. Overall children are much better defenders against upper airway collapse than adults, so their obstructive apnea hypopnea indices (AHI) are lower and OSA severity is scaled differently (Table 11.4) [19].

Association with Obesity

The prevalence of obesity across all age groups has more than doubled in school-aged children and tripled in teens, up to 18% in both age group. Obesity and OSA are independently associated with longer-term adverse cardiovascular, metabolic, and neuropsychological consequences. OSA occurs more often and may be more severe in children and adolescents who are overweight or obese compared with lean children. In a large randomized controlled trial of adenotonsillectomy in school-aged children with adenotonsillar hypertrophy and mild-to-moderate OSA, surgery normalized weight in children who had failure to thrive, but increased in risk for obesity in overweight children [20]. While treatment options for obesity-related OSA includes adenotonsillectomy, "cure" is less likely [5, 21]. Obese teens with OSA have enlarged tonsils and smaller airways compared to lean controls or obese controls without OSA [22]. PAP therapy is generally successful in relieving OSA but limited by generally poor compliance. There is increasing experience with bariatric surgery in youth with extreme obesity which may be a future OSA treatment option to this special population.

Special Populations at Higher Risk for OSA and Obstructive SDB [23–30]

Table 11.5 lists patient groups with genetic, craniofacial, CNS, or neuromuscular disorders who have higher risk of OSA/obstructive SDB due to a combination of factors (craniofacial anatomy, muscular weakness, hypotonia, control of breathing abnormalities, association with obesity).

In some patient groups, PSG is needed to evaluate SDB status before and after prescribing advanced ventilatory support or applying newer medical, surgical, or gene therapies, so key features of these unique patient groups are reviewed.

Table 11.5 Conditions associated with obstructive SDB

Down's syndrome (trisomy 21)
Prader–Willi syndrome
Craniofacial (Pierre Robin sequence, craniosynostoses, Treacher Collins syndrome, cleft lip/palate)
Skeletal dysplasias or connective tissue disorders (achondroplasia, Marfan syndrome)
Sickle cell disease
Neuromuscular disorders (spinal muscular atrophy, Duchenne muscular dystrophy, myotonic muscular dystrophy)
Storage diseases (mucopolysaccharidoses, glycogen storage diseases)
Epilepsy and vagal nerve stimulator

Down's Syndrome [31–34]

Down's Syndrome (also known as trisomy 21) is a common (prevalence 1/800 live births) genetic disorder and the most frequent genetic form of intellectual disability. Hallmarks of the syndrome include intellectual disability, hypotonia, craniofacial abnormalities, short stature, increased incidence of hypothyroidism, and congenital cardiac defects (50% of individuals). Life expectancy is now 60 years. OSA is highly prevalent in children with Down's syndrome (estimates are 30–60% depending on selection criteria) and 90% in adults (almost 70% in the severe range). Worsening of OSA over time is related to increasing age, obesity, and associated hypothyroidism. Predisposing factors for OSA include midfacial hypoplasia, mandibular hypoplasia, small crowded airways, hypotonia, and development of obesity. Symptoms and signs of OSA are underreported by caregivers and managing clinicians. Because sleep disturbances are either unrecognized or thought to be normal in children with Down's syndrome, the American Academy of Pediatrics guidelines for health care supervision in this group recommends referral to a sleep laboratory for polysomnography before 4 years of age [35]. Adenotonsillectomy is the first line of treatment in many cases, but often does not "cure" OSA. PAP therapy is highly effective, can be challenging to implement in this patient group, but often successful with behavioral support. Recognition and treatment of other comorbidities, such as gastroesophageal reflux (GER) in infants, weight management, rhinitis, asthma, or hypothyroidism (seen in up to one-third of children) is essential. Hypoglossal nerve stimulation in another therapy currently under investigation for this patient group. Some specialists have suggested that the increased prevalence of Alzheimer's disease in adults with Down's syndrome may be related in part to hypoxemia and sleep fragmentation from untreated OSA.

Prader–Willi Syndrome [36–42]

Prader–Willi syndrome is a rare (1 in 10,000–25,000 live births) autosomal dominant disorder resulting from the partial deletion or lack of expression of a region of genes on the paternal chromosome 15 or maternal uniparental disomy 15. Clinical features in infancy include diminished fetal activity, infantile hypotonia, and failure to thrive. In early childhood, progressive significant weight gain due to ravenous appetite appears to result in risk for morbid obesity. Other features include short stature, small hands and feet, hypogonadotropic hypogonadism, and intellectual disability. Several features predispose these patients to ventilatory problems: generalized hypotonia, abnormal arousal and ventilatory responses to hypoxia and hypercapnia, scoliosis, and developing obesity. Elevated central apnea indices can be seen in infancy, sometimes with sleep-related desaturation. In childhood and adulthood, obstructive SDB is common. A combination of factors (hypotonia, craniofacial dysmorphism, and viscous secretions) lead to OSA along with adenotonsillar hypertrophy and obesity. Finally, excessive daytime sleepiness (out of proportion to SDB and related to hypothalamic dysfunction) can appear in childhood and affects up to 50% of adults with a narcolepsy-like phenotype. Sleep architecture is also unusual with shorter REM latencies and increased REM cycles. Sleep apnea or sleep disturbance is a minor diagnostic criterion. GH is now routinely prescribed to improve development, growth, and body composition (increased muscle mass and decreased fat mass). Some studies report improvement in resting ventilation and inspiratory drive with this therapy. PSG is often performed prior to GH therapy. Untreated respiratory disorders can contribute to morbidity and premature death in PWS.

Craniofacial Abnormalities [24, 26]

Children with craniofacial syndromes are at high risk for obstructive SDB and OSA. OSA can develop because of both anatomic features that reduce the size of the airway and neuromotor deficits that impair the airway patency during sleep. Midface hypoplasia in children with craniosynostosis and glossoptosis and/or micrognathia in children with Pierre Robin sequence are well-recognized OSA risk factors but the etiology is multifactorial with multilevel airway obstruction. Screening questionnaires for OSA are not validated in this patient population and should not be a surrogate for objective diagnostic testing, so the threshold PSG is low. Some treatments are like those used in healthy children such as adenotonsillectomy, positive airway pressure, positive pressure ventilation, and in refractory cases, tracheostomy. However, distinct treatments include positioning, nasopharyngeal airways, tongue lip adhesion, and mandibular distraction osteogenesis in children with Pierre Robin sequence and midface advancement in children with craniosynostoses.

Pierre Robin Sequence

Pierre Robin sequence (prevalence 1 in 8500–14,000 individuals) is a triad of micrognathia, glossoptosis, and airway obstruction. Infants with this condition are at increased risk of oropharyngeal obstruction and feeding difficulties. About 20–40% of cases of Pierre Robin sequence occur in isolation (by itself) but the rest of cases occur as part of a syndrome that affects other organs and tissues in the body (e.g., Stickler syndrome, Treacher Collins syndrome). Pierre Robin sequence is the most common cause of syndromic micrognathia. Hypoplasia of the mandible leads to OSA due to obstruction at the base of the tongue from glossoptosis and reduced oropharyngeal size.

Cleft Lip/Palate [43]

Cleft lip/palate (1 per 1600 births) is an isolated condition in 70% of cases and part of a syndrome with other anomalies in the rest. Upper airway obstruction is more common in infants who have a cleft palate as part of the Pierre Robin sequence but breathing abnormalities during sleep are seen across the cleft lip/palate spectrum. Most children with cleft palate undergo primary palatoplasty between 9 and 12 months of age, but some children are left with velopharyngeal insufficiency needing further corrective surgery. OSA occurring after surgical correction of velopharyngeal insufficiency is well documented in children with cleft palate.

Craniosynostosis

Craniosynostosis, affecting 1 in 2500 births, occurs as part of a syndrome in 40% of cases. Apert, Crouzon, and Pfeiffer are well-known syndromes with craniosynostosis and are associated with mutations in the fibroblast growth receptor gene. Between 40% and 70% of children with syndromic craniosynostosis will have OSA. Although midface hypoplasia is the predominant causal factor for OSA in these children, multiple other factors such as adenotonsillar hypertrophy and choanal atresia contribute. Central apneas are also reported in some children with craniosynostosis and may be explained by pressure on the respiratory centers due to an underlying Chiari malformation or narrowing of the craniocervical junction.

Treacher Collins Syndrome

Treacher Collins syndrome is a rare (1 in 50,000 live births) autosomal dominant disorder associated with severe OSA. Family history is negative in about 50% of patients. Patients with this syndrome carry mutations in the *TCOF1* gene that encodes instructions for a protein involved in forming bones and other tissues of the face. Classic features include micrognathia, zygomatico-temporo-maxillary dysostosis, mandibular hypoplasia, choanal atresia, underdevelopment of the auricles, down slant of the eyelids, coloboma of the eyelids, and hypoplasia of the zygomatic bone and lateral orbital wall. Abnormalities in these structures explain the high frequency of OSA, 54% in children to 41% in adults. Surgical relief of upper airway obstruction is complicated due to multiple sites of obstruction. Skillful determination of the most useful site(s) for reconstructive surgery is key to a successful outcome.

Skeletal Dysplasias [44–46]

Skeletal dysplasias are rare genetic disorders that affect bones and joints leading to impaired growth and development, leaving affected children with short and/or deformed limbs. *Achondroplasia* is the most common (incidence 1 in 15–40,000 live births) form of disproportionate short stature. Over 80% of individuals with achondroplasia have parents with normal stature and are born with a de novo gene mutation. Two specific gain of function mutations in the fibroblast growth receptor 3 gene cause more than 95% of cases. Clinical features include short stature, shortened limbs, macrocephaly, frontal bossing, and midface hypoplasia. Although life expectancy is near normal, mortality rates are increased at all ages. One-third or more patients may have significant obstructive SDB. Patients with achondroplasia are at higher risk for OSA because of craniofacial dysmorphism, but also at greater risk for central sleep apnea because of cervicomedullary compression. They are also at higher risk for nocturnal sleep–related hypoxemia with or without hypoventilation because of thoracolumbar kyphosis, a small thorax, hypotonia, and tendency for obesity. PSG results are often abnormal and include a range of findings: central apnea, obstructive apneas, hypopneas, gas exchange abnormalities. The American Academy of Pediatrics recommends increased monitoring and evaluation for neurologic signs, especially in the first years of life [47]. Medical and surgical therapies that can improve OSA include adenotonsillectomy, targeted craniofacial surgeries, PAP therapy, and weight management. Other neurosurgeries may be needed for signs of brainstem compression. Evidence-based best practices are not established.

Sickle Cell Disease [48, 49]

Sickle cell disease (SCD), the most common inherited blood disorder in the US, affects 1 in 500 African Americans. It is characterized by chronic hemolytic anemia and complications related to recurrent vaso-occlusion. One of the strongest triggers for vaso-occlusion is oxyhemoglobin desaturation which has been linked to several complications of SCD, such as increased pain, greater risk of CNS events, cognitive dysfunction, history of acute chest syndrome. The prevalence of OSA in children with SCD is higher than in the general pediatric population. Habitual snoring and lower waking SpO_2 values were the strongest OSA risk factors in a cohort study of children with sickle cell anemia, unselected for OSA symptoms or asthma [50]. Because OSA is a treatable condition with adverse health outcomes, greater efforts are needed to screen, diagnose, and treat OSA in the high-risk vulnerable population. Of note, in patient with sickle cell disease, lower than normal SpO_2 values during sleep may not always be true hypoxemia because the oxyhemoglobin dissociation curve for Hb S is shifted to the right, compared to Hb A.

Neuromuscular Diseases

The term neuromuscular disease (NMD) encompasses a large variety of disorders that result in abnormal muscle function. Advances in understanding these diseases, their natural history, and increasing availability of mechanical ventilation for these patients have improved survival. [51, 52] Both spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) are fatal monogenic neuromuscular disorders caused by loss-of-function mutations. The availability of advanced home-based options for ventilatory support and development of novel genetic and molecular therapies [53–56] provides an opportunity to use SDB as an outcome measure while also allowing the use of polysomnography as a validation tool in the assessments of effectiveness of therapies.

Spinal Muscular Atrophy [55, 57–59]

Spinal muscular atrophy (SMA), prevalence 1 in 7000–10,000 live births, is a diverse group of hereditary motor neuron disorders. Most cases are caused by a progressive loss of motor neurons due to the absence of the survival motor neuron (SMN1) protein. Historically five types have been described. Type 1 patients have a fatal course before age 2 years. Type 2 patients live into adulthood, and types 3 and 4 have a normal life span. Especially in type 1 patients, clinical features include progressive proximal weakness with intercostal muscles affected more than the diaphragm resulting in thoracoabdominal asynchrony (paradox) and a bell-shaped chest. Cardiac muscle is not affected. SDB is characterized by hypoventilation related to neuromuscular weakness. However, bulbar dysfunction and acquired maxillary hypoplasia can lead to upper airway obstruction while aspiration, impaired cough, and scoliosis lead to hypoxemia from to lower airway, parenchymal, and chest wall problems. Two novel genetic therapies, an RNA transcript modifier and a gene replacement are changing the natural history of this disease. Infants who historically would have succumbed by age 2 years are now sitting and standing, and some are walking. Children with more advanced disease are either experiencing disease stabilization or a return of recently lost abilities.

Duchenne Muscular Dystrophy [55, 58, 60–63]

Duchenne muscular dystrophy (DMD), affecting 20 per 100,000 live male births, is an X-linked, recessive disorder of the dystrophin gene which supplies structure and function to skeletal and cardiac muscle. Progressive weakness appears around 3 to 6 years of age, wheelchair is needed for mobility by 12 years of age, and scoliosis appears when the patient becomes nonambulatory. Chronic respiratory insufficiency and cardiomyopathy leading to premature death appears in the second decade of life. OSA is the predominant phenotypic of SDB at younger ages, sleep-related hypoventilation at older ages, with significant overlap given the propensity for obesity and variable progression of muscle weakness. Twenty-five percent of unexpected deaths occur at night. There is poor correlation between patient-reported symptoms and the presence of SDB, so the threshold for PSG should be low. PSG is the gold standard evaluation for SDB in children with DMD. Overnight oximetry can show sleep-related hypoxemia, but hypoventilation will be missed by oximetry alone, so PSG must include CO_2 monitoring. Central sleep apnea has been descripted in this patient groups, but it is unclear whether these "central" events are truly central or are classified as central on PSG due to poor signaling in the setting of decreased muscle strength. Noninvasive ventilatory support has changed the natural history, but novel gene therapies are in clinical trials may further improve outcomes.

Myotonic Muscular Dystrophy

Myotonic muscular dystrophy (prevalence 1 in 8000) is an autosomal dominant neuromuscular disease linked to cardiotocography (CTG) repeat expansions of two different genes with variable severity affecting all ages. Features of the adult-onset form of this multisystem disorder include progressive muscle weakness, excessive daytime sleepiness, fatigue, cataracts, endocrine dysfunction, and cardiac arrhythmias [64, 65]. Sleep apnea is highly prevalent. In the rare congenital form, inherited maternally in 90% of cases, infants present with severe skeletal, neuromuscular, and cognitive abnormalities [66]. The mortality rate is high related to need for ventilatory support. The childhood form is later onset and less severe.

Storage Diseases

Mucopolysaccharidosis refers to a heterogeneous group of rare (0.6–5:100,000 live births) genetic lysosomal storage diseases inherited disorders in which the body is unable to properly breakdown mucopolysaccharides with life expectancies of 20 years. Hunter and Hurler syndromes are examples of older names for these conditions. The cardinal abnormalities are musculoskeletal and cardiovascular. Upper airway obstruction is common in all forms of these disorders due to adenotonsillar enlargement, large and protruded tongue, reduced retropalatal and retroglossal space, narrow trachea, narrow airway, short neck, and small thoracic cage. Early recognition of OSA and proper treatment may reduce the high cardiovascular mortality and improve quality of life. There is no cure, but treatments such as bone marrow transplantation and enzyme replacement therapy may help with management of one subtype.

Glycogen storage diseases are caused by defective enzymes involved in the breakdown or synthesis of glycogen. The build-up of glycogen causes progressive muscle weakness and affects the function of the heart, skeletal muscles, liver, and nervous system. Of those, type 2, also known as Pompe disease (1: 40,000 live births) significantly affects respiratory muscles and is associated with SDB. There are three phenotypes based on the amount of residual enzyme activity that present in infancy, childhood, or adulthood. Skeletal muscle weakness and respiratory dysfunction are the hallmarks of the phenotype in adults, and respiratory failure is progressive in all forms. In the infantile form, clinical features of hypotonia, cardiomyopathy, and weakness are present within the first days to months of life.

Enzyme replacement therapy become the standard of care for the treatment of Pompe disease and has been available for more than a decade. The majority of patients with adult onset phenotype show improved ambulatory function and muscle strength, stabilization of pulmonary function, and increased survival that seems to peak at 3–5 years of treatment and is followed by a plateau or secondary decline with considerable individual variation after 10 years [67]. In infants and children with infantile or late onset forms, OSA and hypoventilation are common PSG findings, even in the absence of symptoms, with stabilization and improvements in PSG findings after 3 years of enzyme replacement therapy [68, 69]. They also have improved outcomes in terms of survival, remaining ventilator-free, and cardiac, skeletal muscle, and pulmonary function [70–74].

Epilepsy and Vagal Nerve Stimulators

All types of seizures can occur during sleep and some seizures occur only in sleep. Seizures during sleep can be associated with cardiopulmonary events: ictal and post-ictal apnea, tachypnea, tachycardia, bradycardia, and hypoxemia. Central or obstructive apneas may precede the seizure, occur during the seizure, or be the only clinical manifestation of the seizures. Ictal apnea can potentially contribute to sudden unexpected death in epilepsy which occurs more often during sleep.

Patients with vagal nerve stimulators (VNS) for intractable epilepsy should be screened for SDB. [75] About one-third will develop mild OSA and a small number will develop severe OSA. Apneas, hypopneas, desaturations, and tachypnea have been reported to occur exclusively during VNS activation, but not when the VNS is inactive. VNS may affect breathing either by its effect on the upper airway musculature or by its effect on central control of breathing. Vagal efferent nerves alter neuromuscular signal to the upper airway musculature of the pharynx and larynx, resulting in airway narrowing and obstruction. Vagal projection to the brainstem can also affect the rate and depth of respiration. Severity of the airway obstruction is related to the frequency of the VNS. Treatment needs to be individualized, but options include PAP therapy, changing the VNS settings, or stopping therapy.

Disorders Associated with Central Control of Breathing Abnormalities [76–78]

Central control of breathing abnormalities are a unique part of SDB in childhood. Table 11.6 list conditions associated with central apnea respiratory patterns with or without hypoventilation.

Table 11.6 Conditions associated with central apnea respiratory patterns with or without hypoventilation

Immature control of breathing
High altitude–induced periodic breathing
State-related changes in control of breathing Transition to sleep Low apnea hypocapnia threshold High loop gain High ventilatory response to arousal
Treatment emergent central apnea
Obesity hypoventilation syndrome (usually with another syndrome, e.g., Prader–Willi)
Cardiomyopathy and Cheyne–stokes respiration with congestive heart failure
Medication effect (e.g., narcotic-induced, baclofen, valproic acid)
Impaired central control of breathing/autonomic dysfunction CCHS ROHHAD Familial dysautonomia Rett syndrome
Genetic syndromes (e.g., Prader–Willi syndrome, Joubert syndrome)
CNS malformations or CNS tumors Hindbrain malformations (Chiari I, Chiari II with myelomeningocele) Foramen magnum stenosis or cervical medullary compression
Mitochondrial disorders

Central Sleep Apnea

Central sleep apnea in early infancy is usually part of immaturity of respiratory control. Although the mean central sleep apnea index during sleep is usually under 1/h, some normal children have values up to 4–5 events/h.

Elevated central apnea indices in children are reported in the setting of high altitude [79–82], state-related changes in control of breathing [83], certain genetic or metabolic disorders [84–88], CNS malformation or tumors [89–92], cardiac dysfunction [93], and as a medication effect [94–96]. One group has reported on "idiopathic" central apnea in pediatric patients, but potentially explanatory medical conditions were present [97]. Frequent prolonged (>20–25 s) central apneas, bradypnea with slow respiratory rates for age (rates less than 12/h), extreme elevation of periodic breathing indices or Biot's breathing suggest a problem requiring CNS imaging.

Central Hypoventilation Syndromes [98]

Hypoventilation refers to an increased arterial concentration of carbon dioxide due to inadequate gas exchange. Central hypoventilation means a deficiency in the central nervous system, rather than the respiratory system, is the root of the problem. Central hypoventilation is uncommon and may be due to a variety of conditions which are either congenital or acquired (Table 11.6). Current therapy for central hypoventilation focuses on achieving normal gas exchange, primarily through mechanical ventilatory support. Early identification of central hypoventilation and initiation of ventilatory support can improve adverse outcomes associated with chronic hypoxemia.

CCHS [99–101]

Congenital central hypoventilation syndrome (CCHS) is a rare, lifelong genetic disorder that causes central alveolar hypoventilation. Paired-like homeobox 2B (*PHOX2B*) mutations are found in almost all patients with CCHS. This gene encodes a key transcription factor that regulates neural crest cell migration and development of the autonomic nervous system. Deficiencies in central integration of chemoreceptor inputs cause autonomic dysfunction and loss of respiratory drive in CCHS. In addition, many patients have other symptoms of autonomic dysfunction (e.g., Hirschsprung disease and neural crest tumors) in addition to hypoventilation. Most patients present during the neonatal period, but late onset CCHS may present in later infancy, childhood, or even adulthood under various circumstances (e.g., respiratory infection, anesthesia). Since its original description in 1970 [102], this condition has evolved from a life-threatening neonatal onset disorder to include broader and milder clinical presentations, affecting children, adults, and families. Genes other than *PHOX2B* have been found to cause CCHS in rare cases.

In CCHS, the hypoventilation is worse in sleep compared to wakefulness. CCHS is unique in that it is the only respiratory disorder in which SDB is worse in NREM compared to REM sleep. Hypercapnia is greatest in NREM sleep because intact central chemoreception is essential to support normal ventilation in that state. Hypercapnia is milder in REM sleep and minimal to absent in wakefulness because central chemoreception is less important to ventilatory control in those states. The hypoventilation is caused by a shallow, low tidal volume (2 cc/kg) pattern of breathing rather than recurrent prolonged central apneas or slow respiratory rate. Patients with CCHS have absent or negligible ventilatory and reduced arousal sensitivity to hypercapnia and hypoxemia, so they do not show signs of respiratory distress when challenged with hypercarbia or hypoxia. Residual peripheral chemoreceptor function may allow for adequate ventilation during wakefulness.

Most *PHOX2B* mutations occur de novo, but 5–10% of cases are inherited in an autosomal dominant pattern with variable penetrance depending on the genotype. Most patients (90%) with CCHS will be heterozygous for extra polyalanine repeats in a specific region of the *PHOX2B* gene. The normal genotype is referred to as 20/20, while the mutated proteins produce extra repeats described as 20/24 to 20/33. The length of the polyalanine repeat expansion correlates with disease severity. A larger repeat region is associated with a more severe clinical phenotype more likely to present in the newborn period. In contrast, late-onset CCHS is more likely to be associated with a smaller repeat region and a milder clinical phenotype. The remaining 10% of patients, typically those with the most severe CCHS phenotypes, will be heterozygous for a non-polyalanine repeat-type mutations causing missense, nonsense, or frameshifts in the *PHOX2B* gene. Testing for a *PHOX2B* gene mutation is needed to confirm the diagnosis. Between 5% and 10% of cases are inherited in an autosomal dominant pattern from an affected and/or asymptomatic parent with somatic mosaicism for the expansion mutation. Parents and siblings should also be screened the mutation since there will be a 50% chance of recurrence with each future pregnancy. Genotype–phenotype associations allow for anticipatory guidance and improved clinical care. At present, management relies on lifelong ventilatory support (invasive and noninvasive ventilation and diaphragmatic pacing) and close follow up of dysautonomic progression. Infants with CCHS often require mechanical ventilation 24 h per day until wake–sleep periods are more stable and predictable, so they undergo tracheostomy.

ROHHAD [103–106]

ROHHAD (rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) is a rare disorder that presents between 3 and 10 years of age. Rapid onset weight gain usually occurs first; but hypoventilation, hypothalamic dysfunction, or tumors may bring the patient to medical attention. The hypothalamic dysfunction either precedes or follows weight gain and includes central hypothyroidism, growth hormone deficiency, diabetes insipidus, hyperprolactinemia, precocious/delayed puberty, thermal dysregulation, or corticotrophin deficiency. Once severe hypoventilation develops, ventilatory support is needed. Children are at high risk for respiratory arrest and mortality is high. Children with ROHHAD are also at risk for developing neural crest tumors. Developmental delay, regression, and behavioral problems are common. *PHOX2B* mutations are not seen and no candidate genes have been found. The cause is unknown but may be related to autoimmune inflammation of the CNS. ROHHAD can be diagnosed in children older than 18 months based on the development of rapid weight gain, endocrine defects, and central hypoventilation with other features of hypothalamic dysfunction. Repeated evaluations are needed in children as the syndrome evolves. Treatment is supportive and includes ventilatory support at night, as needed. Unrecognized or inadequately treated hypoventilation may have devastating consequences including death.

Familial Dysautonomia [107–109]

Familial dysautonomia is a rare autosomal recessive disorder affecting infants and children of Jewish Ashkenazi population which has a high carrier rate (1:30). It is caused by a mutation in the *ELP1* gene that encodes scaffold proteins and regulators of different kinases. The discovery of this mutation made prenatal diagnosis possible and resulted in a dramatic reduction in new patients. The pathophysiology is due to progressive autonomic neuropathy (blood pressure and heart rate instability, impaired sensation, swallowing dysfunction, ataxia) associated with progressive loss of small myelinated and unmyelinated fibers. The clinical manifestations may be present at birth. Over time, affected children and adults suffer from cardiovascular, respiratory, gastrointestinal, musculoskeletal, renal dysfunction, and developmental abnormalities. Patients have abnormal ventilatory responses to hypoxia and hypercapnia. Breath-holding spells appear during infancy and persist throughout life. Overall, 91% of pediatric patients and 85% of adults have some degree of SDB (obstructive apnea, central apnea, desaturation, hypoventilation). SDB is a consequence of chemoreflex failure causing impaired ventilatory drive, neuromuscular dysfunction causing or aggravating upper airway obstruction, scoliosis, and chronic lung disease. Untreated sleep apnea is a risk factor for sudden unexpected death during sleep in these patients.

Rett Syndrome [110–114]

Rett syndrome is a rare X-linked genetic disorder (1:10,000 female infants) that typically appears after 6–18 months of age. Symptoms and signs include loss of acquired speech; stereotypic hand movements; deceleration of head and brain growth; autistic behaviors; seizures; scoliosis; dysautonomia in the form of respiratory, cardiac, and gastrointestinal dysfunction; and sleeping problems. More than 95% of girls show a de novo loss of function mutation in the gene for the *MECP2* protein involved in transcriptional silencing and epigenetic regulation of methylated DNA.

Breathing abnormalities are a prominent clinical feature and included in the diagnostic criteria. The classic breathing abnormality in girls with Rett syndrome occurs during wakefulness. It is characterized by rapid shallow breathing (causing hyperventilation), followed by central apnea with breath holding, often followed by profound desaturation and cyanosis. Rett girls can have daily severe breathing abnormalities while awake but breathe more normally when asleep. This unexpected finding suggests an imbalance between the behavioral and metabolic control of respiratory. Rett girls also have markedly impaired sleep–wake patterns (delayed sleep onset, more night waking, and excessive daytime sleep) which may worsen over time but may be amenable to behavioral modification and melatonin. Other night behaviors include nighttime laughter, night screaming, nighttime seizures, and severe bruxism. Approximately 25% of patients die prematurely of cardiorespiratory failure.

Hindbrain Malformations (Chiari I and Spina Bifida) [29, 115]

Chiari I [86, 116–121]

Chiari I malformation, occurring in 1 per 1000–5000 births, includes malformations of the cerebellum and brainstem in which the cerebellar tonsils are displaced below the foramen magnum. Patients with Chiari I malformation may present with headaches, snoring, apnea, and dysphagia. SDB, including obstructive sleep apnea, central sleep apnea, and central alveolar hypoventilation, is estimated to occur in one-quarter of non-syndromic patients. SDB prevalence increases when Chiari I is part of a syndrome with other malformations. SDB is more severe when cervicomedullary compression and/or syringomyelia is present. Compression of the brainstem and respiratory centers is thought to be the mechanism involved in producing central apneas while compression of cranial nerves IX and X leads to decreased upper airway patency and OSA.

Chiari II [92, 122–124]

Spina bifida includes a Chiari II malformation with herniation of the cerebellum and medulla into the spinal canal in association with a myelomeningocele. Over one-half of the children have SDB which is associated with sudden death in young adults. SDB includes central respiratory control abnormalities [apnea (central and/or obstructive), bradypnea, hypoventilation, impaired ventilatory and arousal responses to CO_2 and O_2, breathing holding spells] and restrictive lung disease due to neuromuscular weakness and scoliosis.

CNS Tumors [89]

Medulloblastoma and brainstem gliomas are tumors that can cause both central and obstructive apnea by compression of the respiratory nuclei or cranial nerves that innervate the tongue and pharynx. Tumors that affect the hypothalamus can affect sleep–wake patterns and produce fragmented sleep, increased daytime sleepiness, obesity, and secondary narcolepsy. Medullary nuclei involved in breathing include the dorsal respiratory nucleus (inspiration), the ventral respiratory nucleus (inspiration and expiation), the pre-Bötzinger complex and retrotrapezoid nucleus (respiratory pacemaker), and the nucleus of the tractus solitarius (vagal afferents). Cranial nerves that innervate the tongue and pharyngeal muscles emerge from nuclei in the medulla (hypoglossal nucleus and nucleus ambiguous). Damage to these nuclei by tumor compression or as a complication of surgical resection can affect breathing, producing central or obstructive apnea. Patients treated for CNS tumors may also present with more daytime sleepiness compared to patient treated for other malignancies.

Sleep-Disordered Breathing in Infants [125]

Infants can show a wide range of SDB patterns including: [1] apnea of prematurity, [2] apnea of infancy with central apnea, [3] periodic breathing, and [4] obstructive sleep apnea. Apnea is extremely common in infants decreasing in frequency as central control of breathing matures during the first year of life [126]. Immaturity of the central respiratory control system is a major factor underlying apnea in infants. Fig. 11.2 shows multiple factors that can trigger apnea in infants.

Infants and young children have more variable breathing during REM, including normal central apneas and central events that even occasionally last longer than 20 s [127]. Among healthy full-term infants recorded at home, 43% had central apneas longer than 20 s and 2% had apnea longer than 30 s. Regular breathing is seen in NREM sleep while irregular breathing is typical of REM sleep. Thoracoabdominal asynchrony in REM sleep is normal up to age 2–3 years [128]. Desaturations following these central apneas are typically brief, but can be associated with SpO_2 nadirs below 90%, even in healthy infants [129, 130]. Other factors that predispose infants to respiratory instability include low functional residual capacity, neuronal instability, increase time in REM sleep stage, and lower apneic threshold.

Apnea of Prematurity [131–134]

Immaturity of central control of breathing is major factor in apnea of prematurity. Almost 100% of infants born less than 28-week gestational age will have apnea of prematurity, 25–30% of infants born at 34 weeks, but it is rare in infants born after 38-week gestational age. The earlier the gestational age, the longer apnea of prematurity persists [135]. In former preterm infants, it disappears by the time the infant reaches 44-week postmenstrual age. Especially in former preterm or low-birth-weight infants, external events can trigger apnea spells in infants who were previously stable. For example, there is an increased risk of apnea events within 2–3 days of routine 2-month immunizations, post anesthesia, and in association with RSV infection.

Premature infants have impaired ventilatory and arousal responses to hypercapnia and hypoxia as well as more compliant chest walls, lower end-expiratory volumes, greater distal airway closure, and greater bradycardia in response to stimulation of the carotid bodies by hypoxia. Although apnea of prematurity is often considered a centrally mediated problem with cessation of respiratory effort, pharyngeal upper airway obstruction can precipitate up to 50% of the central apneas. Upper airway collapse can appear at the end of a prolonged central apnea. The infant's highly compliant airway and relative ventilatory instability contribute to the propensity for upper airway obstruction during sleep. Of note, infants have a robust laryngeal chemoreceptor reflex in response to upper airway collapse which is characterized by repeated swallows, central apnea, and bradycardia.

For diagnostic purposes, the American Academy of Sleep Medicine's latest International Classification of Sleep Disorders (ICSD-3) defines "apnea of prematurity" as observed apnea or cyanosis or a detected central apnea, bradycardia, or desaturation on a hospital's cardiorespiratory monitoring, when the infant is <37-week postmenstrual age at the time of presentation [136]. The term "apnea of infancy" uses the same cardiorespiratory signs, but applied to an infant who is now

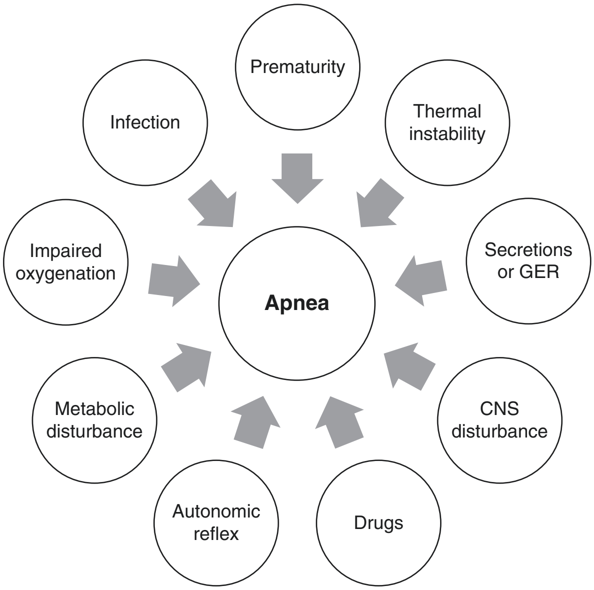

Fig. 11.2 Factors that precipitate apnea in infants

≥37-week gestational or postmenstrual age. Caffeine is effective in the treatment of apnea of prematurity with evidence of long-term safety [137]. Home cardiorespiratory monitoring may be useful as part of an individualized plan for some infants with persistent apnea of prematurity [138].

Periodic Breathing [139]

Periodic breathing, repetitive short cycles of respiratory pauses and breathing, is a normal pattern of breathing that occurs during sleep in most newborns. It is distinct from apnea of prematurity in that it occurs in term as well as preterm infants, peaks later, and lasts longer. Periodic breathing is absent in the first days of life, becomes more frequent at 2–4 weeks postnatal age, then decreases, but may continue for up to 6 months or longer. A major contributing factor to this immature breathing pattern is altered sensitivity to changes in blood oxygen and carbon dioxide content with increased gain in the receptors. In newborns, the PCO_2 apneic threshold is only slightly below the eupneic PCO_2 making these infants more prone to respiratory oscillations and favoring the appearance of periodic breathing [140]. Supplemental oxygen reduces percent time spent in periodic breathing and respiratory instability even in preterm infants with normal baseline SpO_2 values [141]. Of note, oxygen desaturations frequently occur during sleep, and the majority of desaturations are associated with periodic breathing [129, 130, 142]. Periodic breathing is also associated with low lung volumes which predispose toward decreased oxygen reserves and increased intrapulmonary shunting.

Periodic breathing persists longer in infants born at lower gestational age and lower birth weight, but rarely occupies more than 10% of recording time once term postmenstrual age is reached [125, 126, 142]. While periodic breathing is a normal immature breathing pattern in neonates, excessive periodic breathing or an abrupt increase over prior baseline warrants consideration for potential pathology. In older infants and children, elevated periodic breathing outside of wake–sleep transitions can also be a marker for a CNS pathology, hindbrain malformation, or metabolic disorder. Finally, periodic breathing is elevated in any age group at high altitude.

For PSG scoring purposes, periodic breathing is defined as clusters of three or more episodes of central apneas lasting for at least 3 seconds each and separated by ≤20 seconds of normal breathing [143]. Periodic breathing occurs in both REM and NREM sleep. In NREM, periodic breathing is characterized by a regular pattern of pauses separated by consistent intervals of respiratory efforts, while in REM, both irregular and regular patterns are seen. In infants, periodic breathing is more common in REM sleep. In adults (and some children), periodic breathing is most often seen during NREM sleep at sleep onset or sleep-wake transitions.

Apnea of Infancy with Central Apnea [125]

Breathing is irregular in newborns whose respiratory rates are faster and more variable than in older children. Distinguishing between normal and abnormal breathing during sleep can be challenging, especially in infants born prematurely or with congenital abnormalities. For PSG scoring purposes in infants, a central apnea is defined as a prolonged pause in breathing (≥ 20 s) or a shorter pause with physiological corroboration (≥ 3% desaturation, arousal, or bradycardia with heart rate < 60 bpm for at least 15 s). Hypopneas have similar duration and physiological corroboration and require a 30% reduction in airflow or its estimate. Obstructive apneas in infants and children are defined by >90% reduction in airflow lasting at least a two missed breaths in duration (compared with the baseline respiratory rate), but no physiological corroboration is required [143]. Central apneas are common in newborns and infants and central apnea indices are higher, so age appropriate normative data are required to interpret PSG data [144–147].

Terminology: Apnea of Infancy, ALTE, and BRUE

The terminology and the approach to evaluation and management of apnea of infancy has evolved over the last decade. In 1986, NIH Consensus Conference on Infantile Apnea coined the term “apparent life-threatening event (ALTE)” to replace the term “near miss sudden infant death syndrome (SIDS).” [148] An ALTE was defined as an episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid, but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging. In some cases, the observer fears that the infant has died. A broad range of disorders can present as an ALTE including arrhythmias, child abuse, congenital abnormalities, epilepsy, inborn errors of metabolism, and infections. This term was problematic for several reasons. First, for most well-appearing infants with ALTE-like symptoms, the risk of recurrent events or a serious underlying disorder was extremely low. It created a feeling of uncertainty for both the caregiver and clinician. Clinicians felt compelled to perform costly, sometimes risky, often unnecessary tests (including PSG) and to hospitalize the patient even though this management plan often was unlikely to lead to a treatable diagnosis or prevent future events.

In 2016, the American Academy of Pediatrics (AAP) published a clinical practice guideline that recommended replacement of the term ALTE with a new term, "brief resolved unexplained event" (BRUE) [149]. This term describes an event in an infant less than 1 year when the observer reports a sudden, brief, and now resolved episode of at least one of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hyper- or hypotonia); and (4) altered level of responsiveness. Clinicians should diagnosis a BRUE only when there is no explanation for a qualifying event after conducting a history and physical examination. This newer guideline shows an approach to evaluation and management that is based on the risk that the infant will have a repeat event or has a serious underlying disorder. It identifies (1) lower-risk patients based on history and physical examination, for whom evidence-based guidelines for evaluation and management are offered and (2) higher-risk patient, whose history and physical examination suggest the need for further investigation, monitoring, and/or treatment. Overnight PSG was not recommended for the management for infants who met criteria for having experienced a low-risk BRUE. The criteria for a higher-risk BRUE are listed in Table 11.7.

In an updated clinical practice guideline to provide a framework for evaluation of in the higher-risk group, PSG may be considered to characterize and quantify apnea type and is indicated in select patients with prematurity, noisy respirations, or recurrent and/or severe BRUE in whom SDB is suspected [150].

Table 11.7 Higher-risk BRUE criteria [150]

Age < 60 days
Prematurity: Gestational <32 weeks and postmenstrual age < 45 weeks
Recurrent event or occurring in clusters
Duration of event ≥1 min
CPR required by trained medical professional
Concerning historical features
Concerning physical examination findings

SUID, SIDS and Other Sleep-Related Infant Deaths [151, 152]

Each year, 3500 infants die in the US from sleep-related infant deaths, including the following ICD-10 diagnosis categories: sudden infant death syndrome (SIDS), ill-defined deaths, and accidental suffocation and strangulation in bed. SIDS is a sub-category of sudden unexpected infant death (SUID) and a cause assigned to infant deaths that cannot be explained after a through case investigations including autopsy, a scene investigation, and review of clinical history. In 2018, the SUID rate was 90.9 per 100,000 live births with about 1300 deaths due to SIDS, about 1300 deaths due to unknown causes, and about 800 deaths due to accidental suffocation and strangulation in bed. SIDS rates declined significantly from 130.3 deaths per 100,000 live births in 1990 to 35.2 deaths per 100,000 live births in 2018 [153]. After this first decrease in SIDS deaths by more than 50% through several public health initiatives, the overall death rate attributable to sleep-related infant deaths has not declined further. SIDS is still the leading cause of post-neonatal (28 days to 1 year of age) death. These SIDS and SUID mortality rates, like other causes of infant mortality, have notable and persistent racial and ethnic disparities. The rates in non-Hispanic black and American Indian/Alaska Native infant were more than double the rate in non-Hispanic white infants.

The American Academy of Pediatrics updated recommendations for a safe sleep environment (Fig. 11.3) that can reduce the risk of all sleep-related infant deaths includes supine position, the use of a firm sleep surface, room-sharing without bed-sharing, and the avoidance of soft bedding and overheating. Other recommendations for SIDS risk reduction include the avoidance of exposure to environmental tobacco smoke, alcohol, or illicit drugs; breastfeeding; routine immunizations; and use of a pacifier.

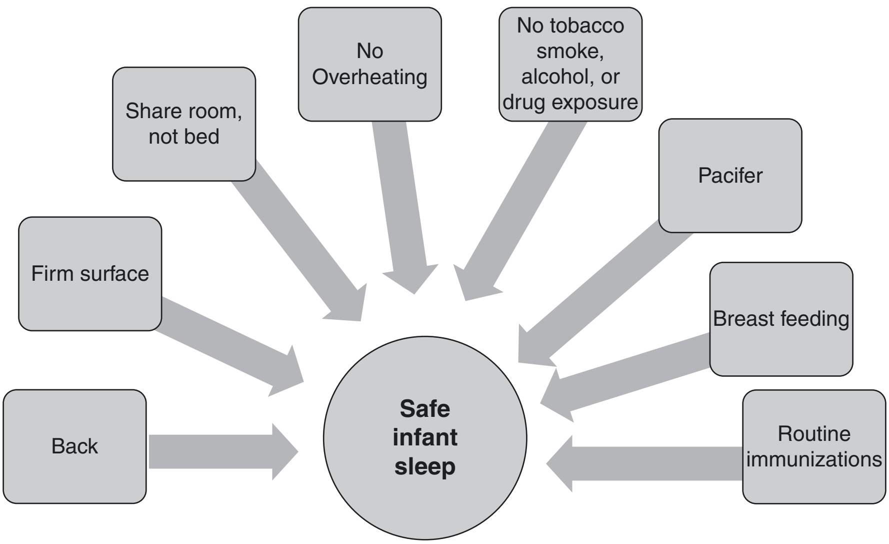

Fig. 11.3 Safe infant sleep

OSA and oSDB Presenting in Infants [3, 19, 154, 155]

Obstructive sleep apnea in infants has a distinctive pathophysiology, natural history, and treatment that is different from older children and adults. Infants are particularly vulnerable to obstructive SDB related to their upper airway structure, adverse pulmonary mechanics, ventilatory control, arousal threshold, laryngeal chemoreflex, and a REM-predominant sleep state distribution. OSA in infants can arise from diverse airway abnormalities extending from the nose to the larynx. Especially in infants, the highly compliant airway and the relative ventilatory instability further contribute to a propensity for upper airway obstruction during sleep. In addition to history of prematurity, other abnormalities that predispose to OSA and obstructive SDB in infants are summarized in Table 11.8.

Table 11.8 Predisposing factors and medical conditions associated with OSA in infants [125, 155]

Craniofacial	**Neurological**
Maxillary hypoplasia	Cerebral palsy
Down syndrome	Chiari malformations
Achondroplasia	Spinal muscular atrophy
Craniosynostosis	Nemaline rod myopathy
Treacher Collins	Mitochondrial disorders
Micrognathia and/or retrognathia	**Respiratory mechanics/ventilatory control**
Non-syndromic Pierre Robin sequence (cleft palate)	High chest wall compliance
Syndromic Pierre Robin sequence (Stickler, Treacher Collins)	Rib configuration round/horizontal
Hemifacial microsomia	Small diaphragmatic zone of apposition
Nager syndrome (acrofacial dysostosis)	High metabolic rate
Macroglossia	NREM apneic threshold close to eupneic CO_2 level
Down syndrome	Ventilation-perfusion mismatch
Achondroplasia	**Miscellaneous**
Beckwith-Wiedemann	Prader-Willi syndrome
Hemangioma, lymphangioma	Mucopolysaccharidoses
Laryngeal	Gastroesophageal reflux
Laryngomalacia	Chronic lung disease of infancy
Vocal cord paralysis	Obesity
Laryngeal webs/cysts; edema	Adenotonsillar hypertrophy
Congenital or acquired subglottic stenosis	Increased REM sleep
Hemangiomas	Neck flexion
Nasal obstruction	Respiratory infection
Choanal atresia or stenosis	Sleep deprivation
Nasogastric tube	Sedating medications
Allergic rhinitis	Maternal smoking during gestation
Upper respiratory tract infection	
Septal deviation	
Nasolacrimal duct cysts	

OSA in infants has been associated with failure to thrive, behavioral deficits, and sudden unexpected death. Especially in infants, the clinical history and physical examination alone are poor predictors of objectively measured upper airway obstruction. Many otherwise healthy infants without obstructive sleep apnea will snore [156]. Snoring has not been found to be predictive of OSA presence or severity in infants with cleft palate and micrognathia [157, 158]. The presence and severity of the OSA can be confirmed by PSG. Infants with severe OSA can have marked hypoxemia, hypoventilation, and/or sleep fragmentation. PSG can be challenging in infants and interpretation requires comparison with normative infant data and consideration of the infant's gestational and postmenstrual ages [159]. Direct endoscopic visualization is essential to show the specific cause of airway collapsibility and critical to selecting the optimal therapy. The management plan should be patient-centered and consider the natural history of the disorder, severity of the OSA, and other co-occurring medical problems and family preferences. A high percentage of infants diagnosed with OSA have a history of prematurity or underlying congenital conditions and require coordination of care by multiple subspecialties [160]. Nonsurgical treatment options can include nasopharyngeal stents, PAP therapy, supplemental oxygen, positional therapy, and treatment of reflux. Surgical options should target the underlying anatomic etiology. Examples include supraglottoplasty for severe laryngomalacia, mandibular distraction for micrognathia, tonsillectomy and/or adenoidectomy for lymphoid hyperplasia, choanal atresia repair, laryngeal reconstruction, and/or tracheostomy. A recent review provides diagnostic and management guidance for obstructive SDB in infants and toddlers less than 2 years of age, including those with complex conditions like Down's and Prader–Willi syndromes [3].

Polysomnography and Diagnostic Testing: Special Considerations in Children [161]

The American Academy of Sleep Medicine (AASM) endorses the usefulness of PSG in the evaluation of SDB in children of all ages. [7, 8] The AASM Scoring Manual supplies guidance for technical PSG performance standards and respiratory and non-respiratory signal scoring rules for infants and children [143]. Table 11.9 takes an updated look at the respiratory indications for PSG in children.

In laboratory, attended PSG has been the "gold standard" for the diagnosis of OSA in children. The American Academy of Pediatrics also recommends that PSG be performed in children with snoring and symptoms or signs of OSA [1] and for high-risk BRUE infants in whom there are clinical concerns for SDB [150]. PSG is also the "gold standard" for diagnosis of pediatric SDB including nocturnal hypoventilation in need of ventilatory support with the goal of identification of SDB before patients become symptomatic [162]. PSG is also helpful in assessing for residual SDB prior to removing a tracheostomy [163].

Table 11.10 summarizes the differences for acquisition, scoring, and reporting of respiratory parameters in children versus adults [143]. In brief, carbon dioxide is measured, respiratory events shorter than 10 s are scored, and periodic breathing and hypoventilation are reported in children. In children, central apneas are scored if they are at least 2 breaths in duration (compared to the child's baseline respiratory rate) and are associated with a ≥ 3% desaturation, an arousal or bradycardia, or are ≥20 second in duration. This differs from adult criteria for scoring central apneas where the duration of the pause must be ≥10 seconds, and

Table 11.9 Updated view of respiratory indications for PSG assessment in children

Diagnosis	Management
OSA	Reevaluate residual OSA, s/p adenotonsillectomy or craniofacial surgery
Central sleep apnea ± hypoventilation[a]	Initiate PAP titration or PAP respiratory support[a]
CCHS or other control of breathing disorders	Evaluate oral appliance
Sleep-related hypoxemia/hypoventilation due to other disorders[a]	Prior to tracheostomy decannulation[a]
Apnea of infancy Higher risk BRUE with concerns for SDB	Reassess adequacy of ventilatory support therapies, noninvasive or via trach[a]

aWith these diagnostic concerns, the sleep laboratory will need CO_2 monitoring equipment (both end-tidal CO_2 and transcutaneous CO_2) and must be prepared to accommodate ventilatory support either noninvasively or via tracheostomy in medically stable patients

Table 11.10 Differences for acquisition, scoring, and reporting respiratory parameters in children versus adults [143]

	Child	Adult
Obstructive	2 missed breaths duration No corroboration required	≥10 s duration No corroboration required
Central	2 missed breaths duration associated with ≥3% desaturation, arousal, or HR <50 for 5 s* If ≥20 s duration, no corroboration needed Score/report periodic breathing * If age < 1 yr., use <60 bpm for 15 s	≥10 s duration Score/report Cheyne–stokes respiratory pattern if criteria met
Hypopnea	2 missed breaths duration ≥30% ↓nasal pressure or back-up associated with ≥3% desaturation or arousal	≥10 sec duration ≥30% ↓nasal pressure + ≥3% desaturation or arousal or ≥30% ↓nasal pressure + ≥4% desaturation
Hypoventilation	>25% total sleep time with CO_2 > 50 mmHg $EtCO_2$ or $tcCO_2$ or arterial Measure/report hypoventilation recommended	↑ CO_2 > 55 mmHg for ≥10 min ↑ CO_2 ≥ 10 mmHg from wake supine to sleep with values >50 mmHg for ≥10 min Report hypoventilation: optional

there is no requirement for associated desaturation, arousal, or bradycardia. Desaturation with central apneas usually shows a decreased pulmonary reserve, while prolonged central apneas are more likely to indicate a CNS abnormality or immature control of breathing. Central apneas are also more common in infants and children because of a vigorous Hering–Breuer reflex characterized by compensatory central respiratory pauses after stimulation of pulmonary stretch receptors following a large breath, such as with a sigh or body movement. Normative respiratory and sleep PSG data are available for infants and children [145–147, 164–170].

When assessing the severity of OSA in children, it is useful to consider the obstructive apnea and hypopneas indices together and separate from the central apnea index. Since central events can be frequent and normal in children (especially post movement, post sigh, in REM sleep, and in transition from waking), they should not contribute to measuring the severity of the obstruction, unless they are clearly related to unmasking of the apnea–hypocapnia phenomenon sometimes seen post arousal or waking after an obstructive event. It is also important to capture baseline cardiorespiratory data in quiet wakefulness prior to the sleep recording to confirm that any abnormal cardiorespiratory findings are truly sleep related, and not just related to the patient's chronic health problems.

PSG, long considered to be the "gold standard" for diagnosis of OSA in children, allows for simultaneous, continuous comprehensive monitoring of sleep, breathing, and other signals and can detect the presence and severity of physiological disturbances. Comprehensive assessment and attended studies may be more important when testing children with complex medication conditions. On the downside, it is expensive, burdensome for families, may not be tolerated by all children, and access is limited to facilities with pediatric expertise.

In the COVID era, pediatric sleep medicine was thrust into telemedicine and HSAT quickly became a safer "option" for selected patients with other options were simply not available. The future role for HSAT in the diagnosis of OSA in children is a topic of active investigation and keen interest to improve disparities in diagnosis, access to care, and treatment outcomes [171–175].

PSG Interpretation in Pediatrics

Compared to adults, healthy children are much better defenders of upper airway patency and have many more normal central pauses. They have healthier lungs with higher baseline oxyhemoglobin saturation values, more robust chemo- and mechano-reflexes, and are less arousable during sleep [19]. These protective factors result in lower obstructive apnea hypopnea indices, higher central apnea indices (especially in infants), less sleep-related hypoxemia, and less sleep fragmentation. In terms of OSA thresholds in children, many pediatric sleep specialists consider an oAHI <1 as "normal," 1–1.99 as "very mild," 2–4.99 as "mild," 5–9.99 as "moderate," and ≥ 10 as "severe."

The obstructive AHI derived from the PSG has been the primary disease defining metric to decide the presence and severity of OSA. However, in the presence of medical comorbidities (e.g., chronic pulmonary conditions, neuromuscular weakness, thoracic cage deformities) some of the respiratory events that meet scoring criteria for hypopneas may not be true signs of upper airway obstruction. Failure to recognize the contribution that lower respiratory tract problems make to scoreable hypopneas in the AHI can lead to overestimation of upper airway obstruction, misdiagnosis of OSA, and inappropriate therapies.

In children, when reviewing all the comprehensive physiologic data contained in a PSG, it is important to "read beyond the AHI." The reader should not only confirm obstructive AHI, but look for other markers of respiratory dysfunction: oximetry metrics (lower baseline SpO_2 values, frequency of desaturation events, time spent with low saturation values); the presence of paradoxical respiratory efforts, tachypnea, or loss of nasal airflow/mouth breathing; determine whether REM supine time was captured, track hypoventilation, unexpected central apneas, respiratory-related arousals or movements; sleep disruption or abnormal sleep architecture; and sinus tachycardia for age or other cardiac arrhythmias. When reviewing PSG studies in children, focusing on the AHI alone as the primary disease-defining metric can lead to an underestimation of sleep disordered breathing especially in the presence of comorbid medical condition. SDB can also be overestimated if normal central pauses that meet AHI scoring criteria are counted as evidence of disease.

Finally, in terms of clinical utility, the read should understand that the oAHI metric has not been the best predictor of OSA-related impairments or their response to treatments like adenotonsillectomy. In fact, OSA symptom scores were better than the oAHI at reflecting OSA-related impairments of behavior, quality of life, and sleepiness and better at predicting improvements after adenotonsillectomy [176].

Accommodating Children in the Sleep Laboratory

Most sleep laboratories are adult-oriented with more than half of AASM accredited sleep center only performing studies in children aged 13 years and above and very few dedicated solely to pediatrics [177]. Specifically for young children or older children and adults with intellectual or developmental disabilities, initiation of PAP therapy will likely require mask desensitization techniques prior to scheduling a titration study [178]. Several references describe best practices for accommodating children and families in the sleep lab [179–181]. Table 11.11 summarizes some of those basics.

Table 11.11 Basics of accommodating children in the sleep laboratory

Know all about the patient who is coming for testing Comorbidities, medications, wake–sleep schedule, mobility concerns, special needs
Create protocols to offer child-friendly and family-centered services For example, allow earlier arrival and later sleep times; lower staff-to-patient ratios, accommodate caregiver
Prepare the child and family for the PSG procedure prior to their arrival
Train staff to work with children and families
Offer comfortable, in-room sleeping arrangements for the parent
Assure availability of pediatric-sized sensors, CO_2 monitoring, PAP masks
Engage the children and caregiver with the PSG procedure
Interpret studies using pediatric normative data
Improve quality by following up with families about their experience

Summary of Key Points

- Sleep-disordered breathing (SDB) in children includes not only obstructive sleep apnea (OSA) related to adenotonsillar hypertrophy in otherwise healthy children, but also OSA in children with complex medical conditions, control of breathing problems (central sleep apnea, hypoventilation), and worsening breathing in sleep in children with genetic, craniofacial, central nervous system, neuromuscular, chest wall, or other chronic pulmonary disorders.
- There are important differences in the clinical presentation, evaluation, PSG approach, and management of OSA between children and adults.
  - The nature of SDB changes in preterm neonates, term neonates, and infants depending on gestational age, chronological age, and postmenstrual age as control of breathing matures and stabilizes over the first year of life.
- The sleep medicine specialist and sleep center should be prepared to comprehensively assess and manage a broad range of sleep-related breathing problems across the age spectrum, from infants to young adults.
- A child-focused and family-centered approach to PSG evaluation of SDB in children is part of best practices for diagnosis and treatment.

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