ERS Statement on obstructive sleep-disordered breathing in 1- to 23-month-old children

ERS Task Force 2012-09

Online Supplementary Appendix

Previously published guidelines on the diagnosis and management of obstructive SDB

Two major guidelines in English concerning the diagnosis and management of obstructive SDB with some reference to children younger than 2 years have been published:

- The American Academy of Pediatrics revised Clinical Practice Guideline and the Technical Report on the Diagnosis and Management of uncomplicated childhood obstructive sleep apnoea syndrome (OSAS) in 2012 [1, 2]. Infants younger than 1 year as well as children with complex abnormalities such as Down syndrome, craniofacial abnormalities or neuromuscular disorders have not been covered.

- The 2009 Royal College of Paediatrics and Child Health Report on Standards for Services for Children with Disorders of Sleep Physiology in Childhood includes only a brief discussion of OSAS[3].

Three major guidelines on the methodology and/or indications of polysomnography have mentioned special problems with children younger than 2 years:

- The 1996 American Thoracic Society guideline for the indications, performance and scoring of polysomnography [4].

- The 2007 American Academy of Sleep Medicine (AASM) guidelines for the indications, performance, scoring and interpretation of polysomnography with an updated version in 2012 [5, 6].

- The 2011 American Academy of Sleep Medicine evidence-based review and practice parameters on respiratory indications for polysomnography in children [7, 8].

However, full polysomnography is not a widely available diagnostic tool. In several centres around Europe, other modalities are also used for the objective diagnosis of obstructive SDB in childhood. Thus, there is clearly a need to summarise evidence for the diagnosis and management of obstructive SDB in settings with limited resources.

Methods

The current ERS document contains a series of questions (topics), formed by consensus of all members during two face-to-face meetings, with answers summarising the relevant literature. A systematic search of the literature was completed by the two chairs of the Task Force to answer the formulated questions. The MEDLINE, Scopus, PsycINFO, EBSCO and CINAHL Databases were searched for the period between January 1970 and December 2016. Key words used were: "adenoidectomy"; "adenoidal hypertrophy"; "adenotonsillar hypertrophy"; "polysomnography"; "sleep apnoea"; "sleep-disordered breathing"; "sleep-related breathing disorders"; "snoring"; "tonsillar hypertrophy"; "tonsillectomy"; "continuous positive airway pressure"; "non-invasive positive pressure ventilation". The search was limited to articles in the English language and to humans aged 1 to 23 months.

In a first round of literature screening, members of the Task Force group screened all the retrieved titles and abstracts for relevancy. Articles on neonates, apnoea of prematurity, OSAS in adults or non-humans or not related to OSAS were excluded. Conference abstracts, letters and case reports were also excluded. In a second round of literature screening, the selected abstracts were distributed among all members by the two chairs of the Task Force. Each abstract was reviewed by one member who read the abstract and the full text if necessary and classified the

abstract according to its relevance to one or more of the nine broad topics of this document: definition of obstructive SDB; risk factors; pathophysiology; symptoms; diagnosis; morbidity; treatment; and treatment of SDB-related morbidity. During this round of literature screening, non-systematic reviews were excluded, whereas systematic reviews and meta-analyses were retained in the pool of articles.

In a third phase, questions were assigned to members of the Task Force randomly. Each question was assigned to two or more members who prepared an initial answer and a table summarising the evidence contained in the pool of articles. Questions, answers (summary of the literature), literature review and evidence tables were consolidated in an initial draft document by the chairs of the Task Force. In the fourth round, the document was discussed in detail during a third face-to-face meeting and a stepwise approach scheme for the management of obstructive SDB reflecting the current practice of the Task Force members was prepared. However, it should be noted that this scheme is not intended as a general recommendation. The product of this meeting was circulated via the internet among all Task Force members for additional suggestions and comments and for checking the accuracy of evidence tables.

The methodological quality of the articles was graded as class I-IV according to the American Academy of Neurology Clinical Practice Guideline Process Manual to which the reader is referred for further details [9]. Briefly, *class I* includes randomised, controlled trials as well as cohort surveys with prospective data collection. *Class II* refers to randomised, controlled trials with methodological weaknesses, cohort studies with retrospective data collection or case-control studies. *Class III* includes cohort studies with well-defined natural history controls or patients

acting as their own controls. *Class IV* refers to cohort studies not including patients with and without the risk factor/disease or not recruiting subjects who received different interventions.

Topics for future research

Topic 1: Recognition of the young child at risk for OSAS

What is not known?

- o There is no high quality evidence indicating that apparent life-threatening events and cyanotic spells in infants may represent symptoms of OSAS.

- o Prematurity and gastroesophageal reflux have not been evaluated as risk factors for OSAS in infancy adequately.

- o Studies exploring the prevalence of OSAS and nocturnal hypoventilation in young children with cerebral palsy are scarce.

- o Studies assessing the frequency of OSAS in infants with Beckwith-Wiedemann syndrome are not available.

- o What is the role of upper airway endoscopy and/or imaging modalities (lateral neck X-ray, CT or MRI of the upper airway) in the evaluation of young children with OSAS?

Topic 2: Recognition of morbidity and conditions frequently co-existing with OSAS in young children

What is not known?

o More studies are necessary to determine the effects of OSAS on the cardiovascular system.

o There is no high-quality evidence for neurocognitive impairement related to OSAS in young children with complex conditions (e.g. achondroplasia, Chiari malformation, Down syndrome, Prader-Willi syndrome).

o Does OSAS directly increase the risk of feeding difficulties and recurrent otitis media in infants?

Topic 3: Objective diagnosis and assessment of OSAS severity

What is not known?

o Few studies have evaluated polygraphy and nocturnal pulse oximetry as alternative diagnostic tools for OSAS in children younger than 24 months.

Topic 4: When is OSAS treated in young children

What is not known?

o Is there a critical upper age limit for initiating treatment in young children with complex conditions that predispose to upper airway obstruction?

o   Future studies should be performed to determine cut-off values of obstructive AHI for offering treatment.

Topic 5: Stepwise treatment approach for OSAS in young children

What is not known?

o   Randomised, placebo-controlled trials using polysomnography as an evaluation tool are necessary to clarify whether anti-reflux medications improve OSAS severity in infancy.

o   What is the efficacy of anti-leukotriene medications and intranasal corticosteroids for the treatment of OSAS in children with adenoidal or tonsillar hypertrophy younger than 2 years?

o   What is the effect of non-invasive positive pressure ventilation (NPPV) on quality of life and symptoms as compared to surgical treatment for OSAS?

o   Do treatment interventions improve OSAS-associated morbidity?

o   There are no studies reporting polysomnography findings after surgical treatment for choanal atresia or nasal pyriform aperture stenosis.

o   There are no clinical trials comparing the efficacy of non-surgical versus surgical interventions for OSAS related to micrognathia.

o   The subgroup of children with mandibular hypoplasia and OSAS who will benefit the most from mandibular distraction osteogenesis should be better defined.

o   Is there an aetiologic link between cervicomedullary compression at the level of the foramen magnum, central sleep apnoea and increased mortality of infants with achondroplasia?

Topic 6: Follow-up, recognition and management of persistent OSAS

What is not known?

o   What are the appropriate diagnostic tools to evaluate OSAS after implementation of the various interventions?

o   How do treatment interventions compare to each other regarding their long-term efficacy in treating OSAS?

o   What is the long-term prognosis of children who are diagnosed with OSAS during the first 23 months of life?

Online Supplementary Tables

Online Supplementary Table S1

Topic 1: Recognizition of the young child at risk for OSAS

1.1. Which symptoms reported by parents are directly related to OSAS?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
a. *Snoring or "noisy" breathing, sleep apnoeas, frequent movements during sleep, mouth breathing and recurrent awakenings*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**

Freeman et al, 2012 [10]	Prospective, cohort study	IV	10,441 children evaluated from the age of 6 months until the age of 81 months.	Parents in the Avon Longitudinal Study of Parents and Children (ALSPAC) reported SDB symptoms by questionnaire for their child at 6, 18, 30, 42, 57, 69, and 81 months of age. Cluster analysis of SDB symptoms (snoring, mouth-breathing, and apnoea) was performed. Five clusters were identified: "normal" (50%) who were asymptomatic; "late snoring and mouth-breathing" cluster (20%) who remained asymptomatic until 4 years old; "early snoring" cluster (10%) and "early apnoea" (10%) cluster with peak symptoms at 6 and 18 months; "all SDB after infancy" (10%) with symptoms peaking from 30 to 42 months. Children with "early snoring" were significantly shorter than "normal" children.

Bonuck et al, 2011 [11]	Prospective, cohort study	IV	12447 children (at the ages of 0.5, 1.5, 2.5, 3.5, 4.75, 5.75, and 6.75 years) whose parents responded to questionnaires on SDB symptoms of the Avon Longitudinal Study of Parents and Children performed in England from 1991 to 1999.	Prevalence of apnoea "always" was 1%-2% at all ages. Frequency of snoring "always" ranged from 3.6% to 7.7%, and of snoring "habitually" from 9.6% to 21.2%, peaking between 1.5- 2.5 years. At the age of 6 years, 25% of children were habitual mouth-breathers.
Piteo et al, 2011 [12]	Cross-sectional study	IV	457 infants aged 0-3 months recruited from the community	Parents completed sleep questionnaire. Habitual snoring (≥3 nights/week) was reported in 9% of infants. Habitual snoring was significantly associated with exclusive formula feeding, maternal concern about child's breathing during sleep and restless sleep for ≥3 nights/week.
Kalra et al, 2006 [13]	Cross-sectional study	IV	681 infants (age 13.7 ± 2.6 months)	Birth cohort from the community. Parents completed questionnaire

				regarding SDB symptoms and presence of environmental tobacco smoke. Atopic status was evaluated by skin-prick test. Snoring ≥ 3 days/week was reported in 15% of infants. Positive atopic status, African-American race and a history of snoring in the father or in the mother were positively associated with the presence of snoring. There was no significant relationship between snoring and environmental tobacco smoke.
Montgomery-Downs et al, 2006 [14]	Cross-sectional study	IV	944 infants and young children aged 2 weeks-2 years	A questionnaire-based survey of parents of infants and young children recruited from the community. Snoring for 2 days/week was reported in 11.8% of participants and ≥ 3 days/week for 5.3% of

				participants. Factors affecting the risk of snoring included: living in a cigarette smoking household; family history of snoring; maternal age; breastfeeding.
Greenfeld et al, 2003 [15]	Prospective, cohort study	IV	29 consecutive infants <18 months of age who underwent polysomnography and were diagnosed with OSAS due to adenotonsillar hypertrophy	A pediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of OSAS symptoms post-treatment was collected. Two infants underwent adenoidectomy only and the rest of them had adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants.

				Other symptoms included: sleep apnoea (72%), frequent movements during sleep (69%), mouth breathing (62%) and recurrent awakenings (38%). Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$ percentile to the $42^{nd} \pm 32^{nd}$ percentile (P <0.001). 14/29 (48%) of the infants dropped two or more major percentiles prior to surgery. Following surgery, significant weight gain with an increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P <0.0001). 5/29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3/5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was

				documented in 6/23 (26%) of infants and repeat adenoidectomy was required.
Leiberman et al, 1988 [16]	Retrospective, cohort study	IV	14 infants younger than 18 months diagnosed with OSAS by polysomnography or nocturnal monitoring	Snoring, apnoea, failure to thrive, developmental delay and recurrent respiratory infections were the most common presenting symptoms. Adenotonsillectomy was accompanied by clinical improvement in 13 patients. In one case, prolonged nasopharyngeal intubation was necessary.

b. History of apparent life-threatening events (ALTE) or brief, resolved, unexplained events (BRUE)

Author, year	Type of Study	Class	Subjects	Methods and findings
Rabasco et al, 2016 [17]	Case-control study	II	107 children (mean age 5.21 ± 0.90 years) with history of ALTE in the first year of life and 115 control children without history of ALTE	A detailed personal and family history was obtained for all participants. All children underwent a general physical examination, an ear-nose- throat assessment and an orthodontic evaluation. A

				clinical score was calculated using the Sleep Clinical Record (SCR). In the ALTE group, snoring (25.2% vs. 6.1%), apnoeas (19.6% vs. 4.3%), restless sleep (31.7% vs. 6.1%), and habitual mouth breathing (35.5% vs. 12.2%) were significantly more frequent than in the control group (P<0.05). The ALTE group had higher frequency of angle class II (27.1% vs. 15.7%), narrow palate (72.9% vs. 51.3%), and Friedman palate position grades III-IV (31.7% vs. 16.6%) than the control group (P<0.05). 38 of 107 (35.5%) children in the ALTE group had a positive SCR score compared with 14 of 115 (12.2%) controls (P < 0.05).
Sanchez et al, 2006 [18]	Retrospective, cohort	IV	320 patients (10 days to 21	All participants underwent

	study			months old; 74% younger than 3 months; 58% male; 84% born full-term) were recruited sequentially and prospectively for history of apnoea and/or cyanosis.	diurnal or nocturnal polysomnography. 69% of studies were performed overnight. The median apnea index for all the study population was 1.01 episode/h (range 0.1-9.1); 34 patients had at least 1 obstructive apnoea.
Harrington et al, 2002 [19]	Prospective, cohort study	III	10 infants with history of apparent life-threatening events (14 ± 3 weeks old) and 12 age-matched control subjects.	All participants underwent six to eight 45^0 head-up tilts and overnight polysomnography with noninvasive beat-to-beat blood pressure measurement. All control infants had normal polysomnography findings. 50% of the infants with history of apparent life-threatening events had OSAS (more than two obstructive apnoeas per hour of sleep, with short hypoxic events). In slow wave sleep and in response to the tilt, infants with OSAS and history of

				apparent life-threatening event (n=5) had reduced heart rate response, altered heart rate and blood pressure variability and three of the five showed marked postural hypotension. Those infants with history of apparent life-threatening events and without OSAS were similar to controls in terms of cardiovascular responses to the head-up tilt.
Guilleminault et al, 2000 [20]	Retrospective, cohort study	III	346 infants with history of apparent life-threatening events evaluated over a 10-year period and 46 age-matched healthy infants as controls.	Participants had recording of symptoms and signs related to SDB, sleep/wake evaluation, systematic evaluation of the face and naso-oro-pharynx, nocturnal polygraphy and follow-up evaluation.42.6% of the patients had normal nocturnal polygraphic recording and were not different from controls at

				the initial evaluation and during follow-up. Obstructive breathing during sleep was demonstrated in 57.4% of patients and two-thirds of these infants had SDB symptoms and mild facial dysmorphia which was apparent at 6 months of age.
Guilleminault et al, 1992 [21]	Retrospective, cohort study	IV	25 full-term infants with history of apparent life-threatening events in the ages of 3 weeks to 4.5 months who developed OSAS by the age of 5 years and two groups of infants with short-lived symptoms.	Infants who developed OSAS had more frequently a positive family history of OSAS and an early report of snoring or noisy breathing during sleep.
Guilleminault et al, 1984 [22]	Retrospective, cohort study	IV	5 full-term infants with history of "near miss" sudden infant death syndrome at the age of 3-12 weeks.	Infants underwent polygraphy regularly up to the age of 4 years and were monitored at home with a cardiorespiratory monitor. All five subjects developed OSAS

				symptoms. The diagnosis of OSAS was confirmed by polygraphy. Four of 5 infants had adenoidectomy at the age of 3-4 years and they improved significantly.
Guilleminault et al, 1979 [23]	Case-control study	III	29 full-term infants with history of "near miss" sudden infant death syndrome and 30 normal control infants.	Twenty-nine full-term near miss for sudden infant death syndrome (SIDS) and 30 normal underwent 24-hour polygraphy. The 2 groups were compared in terms of central, mixed, and obstructive apnoeas and periodic breathing. Comparisons revealed that between 3 weeks and 4.5 months of age cases and controls differed in the number of mixed and obstructive apnoea (>3 sec) during total sleep time.
c. *Unclear whether gastroesophageal reflux or history of prematurity are associated with OSAS*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Qubty et al, 2014 [24]	Retrospective, cohort	IV	139 infants (aged 0-17	OSAS severity was

	study			months) with clinical features of OSAS who had polysomnography. Subjects with central apnoeas >50% of total number of apnoeas were excluded.	classified as: mild (AHI <5 episodes/h; 30% of patients), moderate (5-9 episodes/h; 30% of patients) or severe (AHI ≥ 10 episodes/h; 40% of patients). Mean weight percentiles were 45th, 34th and 21st, respectively; 33% of infants had weight percentile ≤3rd and 53% of them had severe OSAS. Comorbidities included gastroesophageal reflux (68% of patients), periodic limb movements during sleep (42%), craniofacial abnormalities (37%), neuromuscular abnormalities (34%), history of prematurity (29%), genetic syndromes (29%), laryngomalacia and/or tracheomalacia (27%) and epilepsy (17%). The most commonly seen genetic syndrome was Trisomy 21 and others were achondroplasia, Prader-Willi syndrome,

				Pierre Robin sequence, Crouzon syndrome, de Lange syndrome, mitochondrial disorder, Otopalatodigital syndrome, and Joubert syndrome
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. The average age at follow-up was 7.7 ± 7 months.	40 (41%) had mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h); 30% of patients had gastroesophageal reflux. 47 patients (48%) were observed or received anti-reflux medications; 27 patients (25%) required non-surgical intervention (CPAP in 85% of cases and oxygen therapy in 15% of patients); 36 patients (37%) were treated primarily surgically (tonsillectomy,

				adenoidectomy, adenotonsillectomy, supraglottoplasty, mandibular distraction, total calvarial release of suture, and sublabial repair). 38 patients were followed up with repeat polysomnography after a median interval of 8 months (range 1-24 months) and 68% of infants had resolution of symptoms; 27 infants were followed clinically after a mean interval of 5 months (range 1-34.5 months) and symptoms resolved in 85% of patients. The likelihood of symptom resolution was higher with surgical management than with oxygen therapy/CPAP (OR 4.75; P <0.01) but it did not differ significantly between medical management and oxygen therapy/CPAP (P>0.05). The likelihood of symptom resolution did

				not differ between patients who received medications and those with surgical treatment (P >0.05). Symptom improvement was more likely in children who underwent medical or surgical treatment compared to no treatment (OR 4.57; P=0.01 and OR 7.24; P=0.002, respectively).
Wasilewska et al, 2004 [26]	Retrospective, cohort study	IV	24 children (10 female; ages 2 months-3 years) with sleep disturbances indicating gastroesophageal reflux were recruited.	Polysomnography and 24-h esophageal monitoring were carried out. AHI in active/REM sleep and quiet/NREM sleep was compared between children with nocturnal acid reflux (13 children; 6 female) and controls without nocturnal acid reflux (11 children; 4 female). Children with nocturnal reflux had higher obstructive AHI during REM sleep than controls: 23.35 ± 19.1

				episodes/h vs. 4.99 ± 3.12 episodes/h.
Arad-Cohen et al, 2000 [27]	Retrospective, cohort study	IV	67 infants (<6 months old) with history of idiopathic apparent life-threatening event	All participants underwent polysomnography and pH monitoring. 32 infants did not have reflux (pH < 4 for more than 6 seconds) whereas 14 others had prolonged episodes of reflux and their relationship with apneic events could not be clarified; 21 remaining infants had discrete episodes of apnoea and reflux. In 81% of the apnoeic episodes, no relationship to reflux was noted. Of note, apnoea preceded reflux in 93.6% of the episodes, in only 6.4% of cases the apnoeic episodes followed reflux. When apnoea occurred prior to reflux, the apnea was obstructive in 66.8% of cases and mixed in 33.2% of cases. There

				were no episodes of central apnoea preceding reflux.

1.2. Is delayed growth a frequent clinical presentation in young children with upper airway obstruction?

Author, year	Type of Study	Class	Subjects	Methods and findings
Bonuck et al, 2009 [28]	Systematic review and meta-analysis	-	20 cohort studies describing changes in weight, height, IGF-1 and/or IGFBP-3 serum-levels as z-scores, percentiles or raw data following adenotonsillectomy were reviewed. Studies ranged in numbers of participants from 14 to 204 children and ages of 5 months to 15.8 years with follow-up of 1 month to 3 years.	6 of 20 studies reported growth failure in a proportion of their participants. Results of meta-analysis regarding postoperative changes compared to preoperative values were reported. Standardised height (10 studies; n=363): pooled standardised mean differences (SMD) = 0.34 (95% CI 0.20-0.47); standardised weight (11 studies; n=390): pooled SMD = 0.57 (95% CI 0.44-0.70); IGF-1 (7 studies; n=177): pooled SMD = 0.53 (95% CI 0.33-0.73); IGFBP-3: (7

				studies; n=177): pooled SMD = 0.59 (95% CI 0.34 to 0.83).
Greenfeld et al, 2003 [15]	Prospective, cohort study	IV	29 consecutive infants <18 months of age who underwent polysomnography (PSG) and were diagnosed with OSAS due to adenotonsillar hypertrophy	A pediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of OSAS symptoms post-treatment was collected. Two infants underwent adenoidectomy only and the rest of them had adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants. Other symptoms included: sleep apnoea (72%), frequent movements during sleep (69%), mouth

				breathing (62%) and recurrent awakenings (38%). Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$ percentile to the $42^{nd} \pm 32^{nd}$ percentile (P<0.001). 14/29 (48%) of the infants dropped two or more major percentiles prior to surgery. Following surgery, significant weight gain increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P<0.0001). 5/29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3/5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was documented in 6/23 (26%) of infants and repeat adenoidectomy was required.

Freezer et al, 1995 [29]	Retrospective, cohort study	IV	38 infants who undwerwent adenotonsillectomy over a 5-year period	Complete data were available for 29 (76%) of the 38 infants. Prior to surgery, all infants had OSAS symptoms and 52% of them had failure to thrive. Seven infants were dysmorphic: 3 had Down syndrome, 3 had a craniofacial anomaly and 1 infant had Mobius syndrome. Postoperatively, 79% of patients had complete resolution of OSAS symptoms, but 2 infants with Down syndrome required a tracheostomy to relieve persistent upper airway obstruction; 87% of the infants with pre-operative failure-to-thrive had a significant increase in weight gain velocity from 195.1 ± 80.8 g/month to 509.8 ± 249.1 g/month; $P < 0.001$) irrespective from severity of symptoms. The weight gain velocity of infants

| | | | | without failure to thrive pre-operatively did not change significantly after adenotonsillectomy. No significant changes were noted in linear growth velocity of any infant postoperatively. |
| Leiberman et al, 1988 [16] | Retrospective, cohort study | IV | 14 infants younger than 18 months diagnosed with OSAS by polysomnography or nocturnal monitoring. | Snoring, apnoea, failure to thrive, developmental delay and recurrent respiratory infections were the most common presenting symptoms. Adenotonsillectomy was accompanied by symptom and sign relief in 13 patients. In one case, prolonged nasopharyngeal intubation was necessary. |

1.3. Which findings from the physical examination are related to OSAS in 1-23 month-old children?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Qubty et al, 2014 [24]	Retrospective, cohort study	IV	139 infants (0-17 m.o.) with clinical features of	OSAS severity was classified as: mild (AHI <5

			OSAS who had polysomnography. Subjects with central apnoeas >50% of total number of apnoeas were excluded.	episodes/h; 30% of patients), moderate (5-9 episodes/h; 30% of patients) or severe (AHI ≥ 10 episodes/h; 40% of patients). Mean weight percentiles were 45th, 34th and 21st, respectively; 33% of infants had weight percentile ≤3rd and 53% of them had severe OSAS. Comorbidities included gastroesophageal reflux (68% of patients), periodic limb movements during sleep (42%), craniofacial abnormalities (37%), neuromuscular abnormalities (34%), history of prematurity (29%), genetic syndromes (29%), laryngomalacia and/or tracheomalacia (27%) and epilepsy (17%).The most commonly seen genetic syndrome was Trisomy 21 and others were achondroplasia, Prader-Willi syndrome,

				Pierre Robin sequence, Crouzon syndrome, De Lange syndrome, mitochondrial disorder, Otopalatodigital syndrome, and Joubert syndrome
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥ 1 episode/h) over a 7-year period. The average age at follow-up was 7.7 ± 7 months.	The indication for requesting polysomnography was snoring (53%), nocturnal desaturations (24%), an abnormal pneumogram (5%), suspected apparent life-threatening event (5%), screening for sleep disordered breathing (4%), hypoventilation (3%), diaphragmatic flutter (2%), failed car seat testing (2%), suspected apnoea of prematurity (1%), and as a routine test before growth hormone treatment (1%). Co-morbid conditions

				included gastro-esophageal reflux (30%), laryngomalacia (24%), and craniofacial abnormalities (16%); genetic abnormalities were also present in 53% of infants and trisomy 21 was the most common of them. 40 (41%) infants had mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h).
a. *Adenoidal or less frequently tonsillar hypertrophy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Greenfeld et al, 2003 [15]	Prospective, cohort study	IV	29 consecutive infants <18 months of age who underwent polysomnography (PSG) and were diagnosed with OSAS due to adenotonsillar hypertrophy	A pediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of OSAS symptoms post-treatment was collected. Two infants underwent adenoidectomy only and the rest of them had

				adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants. Other symptoms included: sleep apnoea (72%), frequent movements during sleep (69%), mouth breathing (62%) and recurrent awakenings (38%). Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$ percentile to the $42^{nd} \pm 32^{nd}$ percentile (P <0.001). 14/29 (48%) of the infants dropped two or more major percentiles prior to surgery. Following surgery, significant weight gain increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P <0.0001).

				5/29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3/5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was documented in 6/23 (26%) of infants and repeat adenoidectomy was required.

b. *Nasal obstruction*

Author, year	Type of Study	Class	Subjects	Methods and findings
Samadi et al, 2003 [30]	Retrospective, cohort study	IV	78 children (newborn-18 years) with choanal atresia who were managed in an academic pediatric hospital.	Patients had an average follow-up of 35 months. Thirty-five children (45%) had unilateral atresia, and 43 children (55%) had bilateral atresia. Concomitant disorders were noted: otitis media with effusion (32%), upper and lower airway diseases (32% and 23%), cardiac anomalies (19%), and

				gastrointestinal tract disorders (18%). Presence of bilateral choanal atresia was significantly associated with cardiac disorders (P =0.04), CHARGE syndrome (P=0.002), OSAS (P=0.003), haematological problems (P =0.001), and prematurity or failure to thrive (P =0.006). Airway patency was established surgically in all cases. Average age at the first surgical procedure was 25.2 months for unilateral atresia and 2.4 months for bilateral atresia.
Abreu e Silva et al, 1986 [31]	Prospective, cohort study study	IV	10 infants: 5 with upper respiratory infection; 5 with metabolic alkalosis due to vomiting	Infants underwent 3-4 hours of polygraphy during the illness after after recovery from their illness. During upper respiratory infection, brief (greater than 3 less than 6 seconds) or prolonged (greater than 6 seconds)

| | | | | episodes of obstructive apnoea were recorded. Frequency of gross body movements was increased. In participants with metabolic alkalosis frequency of central apnoea was significantly increased compared to recovery or to case control data. Prolonged (greater than 15 seconds) episodes of central or obstructive apnoea (greater than 6 seconds) were observed during illness. Frequency of gross body movements and periodic breathing were increased. |

c. *Laryngomalacia*

Author, year	Type of Study	Class	Subjects	Methods and findings
Qubty et al, 2014 [24]	Retrospective, cohort study	IV	139 infants (aged 0-17 months) with clinical features of OSAS who had polysomnography. Subjects with central apnoeas >50% of total number of apnoeas were	OSAS severity was classified as: mild (AHI <5 episodes/h; 30% of patients), moderate (5-9 episodes/h; 30% of patients) or severe (AHI ≥ 10 episodes/h; 40% of

			excluded.	patients). Mean weight percentile were 45th, 34th and 21st, respectively; 33% of infants had weight percentile ≤3rd and 53% of them had severe OSAS. Comorbidities included gastroesophageal reflux (68% of patients), periodic limb movements during sleep (42%), craniofacial abnormalities (37%), neuromuscular abnormalities (34%), history of prematurity (29%), genetic syndromes (29%), laryngomalacia and/or tracheomalacia (27%) and epilepsy (17%). The most commonly seen genetic syndrome was Trisomy 21 and others were achondroplasia, Prader-Willi syndrome, Pierre Robin sequence, Crouzon syndrome, De Lange syndrome, mitochondrial disorder, Otopalatodigital syndrome, and Joubert

				syndrome
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. The average age at follow-up was 7.7 ± 7 months.	The indication for requesting polysomnography was snoring (53%), nocturnal desaturations (24%), an abnormal pneumogram (5%), suspected apparent life-threatening event (5%), screening for SDB (4%), hypoventilation (3%), diaphragmatic flutter (2%), failed car seat testing (2%), suspected apnoea of prematurity (1%), and as a routine test before growth hormone treatment (1%). Co-morbid conditions included gastro-esophageal reflux (30%), laryngomalacia (24%), and craniofacial abnormalities (16%); genetic abnormalities were also present in 53% of infants and Trisomy 21 was the

				most common of them. 40 (41%) infants had mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h).
Powitzky et al, 2011[32]	Retrospective, cohort study	IV	20 infants (aged <1 year) who underwent supraglottoplasty for severe laryngomalacia (failure to thrive or signs of severe respiratory distress, such as cyanotic spells, severe intercostal retractions, or prolonged apnoeas with significant desaturations while awake) or moderate laryngomalacia (stridor and associated retractions or dysphagia).	Patients underwent polysomnography pre- and post-supraglottoplasty. Outcome measures included changes in stridor, sleep-disordered breathing, swallowing, and polysomnography parameters before and after surgery. Statistically significant improvements were demonstrated postoperatively in median AHI (-6.4 episodes/h; P=0.02).
Dickson et al, 2009 [33]	Retrospective, cohort study	IV	201 infants with laryngomalacia treated at a pediatric tertiary care center	Of 201 infants, 104 (51.7%) were had a secondary airway lesion (subglottic stenosis in

				38.8%; tracheomalacia in 37.8%). Of those with severe laryngomalacia, 30 (79%) had a secondary lesion, as compared with 51 (61.5%) of those with moderate and 23 (28.8%) of those with mild laryngomalacia. Among infants with mild or moderate disease, those with secondary airway lesions were more likely to require surgical intervention than infants without lesions (27% versus 5.6%; P = 0.0002). The incidence of gastroesophageal reflux was 65.6%. Infants with a secondary airway lesion were more likely to have reflux than those without a secondary airway lesion (84.6% versus 45.4%; P<0.0001).
O' Connor et al, 2009 [34]	Retrospective, cohort study	IV	10 children with moderate-to-severe	Polysomnography was performed before and after

			laryngomalacia who underwent supraglottoplasty with mean age at first presentation of 2 months and 19 days (range 30–134 days)	surgery. The mean time from preoperative polysomnography to supraglottoplasty was 12.1 days and from supraglottoplasty to post-operative polysomnography 83.2 days. The observed anatomical abnormalities were: short aryepiglottic folds (10/10 patients); prolapsing arytenoid mucosa (9/10); and prolapsing or omega-shaped epiglottis (4/10). Total sleep time increased from a mean of 382 min to 475 min (P=0.049) and SpO_2 from a mean of 74.8% to 87.6% (P=0.006); obstructive AHI decreased from a mean of 42.7 episodes/h to 4.47 episodes/h (P=0.009) and respiratory disturbance index from 49.9 episodes/h to 8.36 episodes/h (P=0.002), following supraglottoplasty. A non-

				significant improvement in mean transcutaneous carbon dioxide ($TcCO_2$) partial pressure occurred (57.1 mmHg to 52.8 mmHg) (P=0.259).
Zafereo et al, 2008 [35]	Retrospective, cohort study	IV	Ten infants with laryngomalacia and OSAS who underwent supraglottoplasty.	All 10 patients were extubated after the procedure and there were no peri- or postoperative complications. Postoperative nocturnal polysomnography was performed at 11 weeks postoperatively (range 2-29 weeks). Caregivers reported mild improvement (10%), significant improvement (70%), and complete resolution (20%) of stridor and snoring at 4 weeks after discharge. Marked improvements and statistically significant improvements were recorded in obstructive apnoea index, obstructive

				AHI, respiratory disturbance index and oxygen saturation of haemoglobin nadir (P <0.05).
Valera et al, 2006 [36]	Case series		IV	7 children with mean age 6.8 months (range 1-15 months) with severe laryngomalacia based on symptoms and flexible endoscopy	Four of the 7 children had a history of stridor, and in 3 patients without stridor the predominant symptom of upper airway obstruction was snoring. There was history of cyanosis on effort and increased nocturnal work of breathing or apnea. Baseline polysomnography was performed and subsequently patients underwent epiglottoplasty with bilateral incision of the aryepiglottic folds, followed by bilateral excision of excess mucosa in the lateral arytenoid region. If epiglottis had a posterior position, epiglottopexy was carried

				out. Polysomnography was repeated postoperatively. Preoperatively, one of 7 patients had moderate OSAS and the remaining children had severe OSAS and all of them had paradoxical breathing; RDI was 5.4 to 22.8 episodes/h (mean ± SD: 11.66 ± 7.51 episodes/h); minimum SpO_2 was 70% to 94% (mean ± SD: 81.71% ± 8.47%). Two of 7 patients with pharyngolaryngomalacia did not tolerate extubation and required tracheostomy. Of the remaining patients, 4 had marked improvement of respiratory symptoms and 1 only partial improvement of apnoea and stridor; 2 patients with feeding difficulties did not require a nasogastric tube postoperatively. At an average of 82 days after surgery, respiratory

				disturbance index decreased from a mean of 10 episodes/h preoperatively to a mean of 2.2 episodes/h (P <0.05); minimum SpO_2 tended to increase from 83.2% preoperatively to 86.4% postoperatively (P=0.07). Resolution of OSAS (respiratory disturbance index <1 episode/h) was not achieved in 3 patients with additional abnormalities: tracheomalacia; marked neurologic deficit; hypertrophy of the pharyngeal and palatine tonsils.
Goldberg et al, 2005 [37]	Case series		IV	39 children with median age 15 months (range 1-126 months) who had OSAS (AHI ≥1 episode/h); 16 children ≤24 months; 17 patients were hypotonic and 22 had normal muscular tone	A flexible fiberoptic bronchoscope was used. Abnormalities were categorized in: fixed (narrow nostrils; adenoidal hypertrophy; tonsillar hypertrophy; tongue enlargement) and dynamic

				(inspiratory pharyngeal collapse at the glottis entrance; laryngomalacia). Most frequent fixed airway abnormalities were: adenoidal hypertrophy (64%) and tonsillar hypertrophy (31%). The reported dynamic abnormalities were: laryngomalacia (44%) and inspiratory pharyngeal wall collapse (38%). A large proportion of patients (41%) had both dynamic and fixed abnormalities. 16 of 17 (94.1%) patients with laryngomalacia had associated abnormalities: 5 had pharyngeal wall collapse; 6 had adenoidal hypertrophy; and 5 had both. Only 5 patients with laryngomalacia had stridor.

| Mitchell et al, 2003 [38] | Retrospective, cohort study | IV | 23 children with Down syndrome aged 1 day–10.2 years (median age: 6 months) referred for evaluation of upper airway obstruction 11 with PSG, no description of sleep parameters or AHI index | The most common diagnostic procedure was flexible laryngoscopy; 10 children had laryngomalacia and 1 child was diagnosed with tracheomalacia. Eight patients were evaluated by bronchoscopy and 4 of them had laryngomalacia and episodes of cyanosis. Eleven children had OSAS (48%), 8 of whom were >2 years old; 73% of children with OSAS had recurrent otitis media. Gastroesophageal reflux was a comorbidity in 14 children (61%). Chronic lung disease was present in 13 children (56%), 6 of whom were preterm. Congenital heart disease was present in 11 children (48%) and pulmonary hypertension in 7 children (30%). |
| Roger et al, 1995 [39] | Retrospective, cihort | IV | 985 children who | 115 (11.6%) children had |

			underwent upper airway endoscopy for laryngomalacia.	epiglottoplasty endoscopically. Median age at surgery was 3.6 months (range: 8 days to 4 years); 77% of patients were younger than 6 months. OSAS was demonstrated in 11.3% of patients. The average time of postoperative follow-up was 30 months. Complete resolution of symptoms was noted in 53% of cases. Among 50 patients who underwent blood gas analysis before and after surgery: 58% had normalisation of both oxygenation and ventilation; 22% had normalization of one parameter and improvement of the other; and 20% had improvement of both parameters without normalization.
study				
Marcus et al, 1990 [40]	Retrospective, cohort study	IV	6 patients with severe laryngomalacia who	4 patients had history of life-threatening episodes

			underwent epiglottoplasty at the age of 10.3 ± 5.3 (SEM) months.	of airway obstruction prior to surgery (2 underwent endotracheal intubation; 1 required cardiopulmonary resuscitation; 2 had failure to thrive and 2 were diagnosed with cor pulmonale). Polysomnography was performed during a daytime nap both before and after epiglottoplasty. Preoperatively, 6 children had OSAS, 4 had hypoxaemia ($SpO_2 < 90\%$ while breathing room air), and 4 had hypoventilation (end-tidal carbon dioxide pressure >45 mm Hg). Postoperatively, patients were intubated for 25 ± 7 hours and were discharged after 4 ± 1 days. Follow-up polysomnography was performed 2.8 ± 1.0 months after surgery and was improved in all patients: 2 patients had residual, mild episodes of obstructive sleep apnoea,

				and 1 patient had mild hypoventilation and desaturation. Life-threatening events did not occur in any patients and no further hospitalisations were required.
Holinger et al, 1976 [41]	Retrospective, cohort study	IV	389 infants, children and adults with partial or complete bilateral abductor vocal cord paralysis	149 patients were infants and children 12 years of age or younger; 240 patients had age of 13 years or older. In infants and children the paralyses were congenital in 82 cases; 43 of them were associated with other congenital anomalies. Fifty-nine cases were considered secondary to underlying congenital anomalies (meningomyelocele, Arnold-Chiari malformation, and hydrocephalus). Eight cases of paralysis in this age group were idiopathic. Of the 240 adult cases of

				bilateral vocal cord paralysis. 138 cases occurred following thyroidectomy. The characteristic symptoms of bilateral abductor vocal cord paralysis include normal or near normal phonation with inspiratory stridor which may progress to complete respiratory obstruction. This clinical presentation may be due to the stationary but flaccid midline position of the vocal cords which allows phonation, where they both obstruct the airway and produce a rather clear voice or cry.
d. *Syndromic craniosynostosis with midface hypoplasia (Apert syndrome, Crouzon syndrome, Pfeiffer syndrome) or without midface hypoplasia (Muenke and Saethre-Chotzen syndrome and complex craniosynostosis)*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by

				midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A polysomnogram was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the polysomnogram was repeated within 3–6 months. OSAS was defined as obstructive AHI $\geq$ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI ≥ 25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were

				treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.
MacLean et al, 2012 [43]	Cross-sectional study	IV	50 infants with cleft lip and/or palate prior to surgery aged 2.7 ± 2.3 months; 56% were male, and 30% had a clinical diagnosis of Pierre Robin sequence or a syndrome.	Demographics, clinical history, sleep symptoms, facial measurement and polysomnography data were recorded. 75% of infants snored frequently or constantly. The frequency of parent-reported difficulty with breathing during sleep was 10% for infants with

				isolated cleft lip and/or palate, 33% for those with a syndrome, and 43% for infants with Pierre Robin sequence (P <0.05). All infants had an obstructive-mixed apnoea-hypopnoea index (OMAHI) >1 episodes/h, and 75% had an OMAHI >3 episodes/h. Infants with Pierre Robin sequence had higher OMAHI (34.3 ± 5.1 episodes/h) than infants with isolated cleft lip and/or palate (7.6 ± 1.2 episodes/h) or infants with syndromes (15.6 ± 5.7 episodes/h; P <0.001). Multivariate analysis demonstrated that Pierre Robin sequence was associated with higher OMAHI (P=0.022).
e. *Marked mandibular hypoplasia (e.g. Pierre Robin sequence)*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Rathe et al, 2015 [44]	Retrospective, cohort study	IV	48 infants with Pierre Robin sequence treated	14.6% of infants had syndromic Pierre Robin

			over an 11-year period	sequence. 62.5% of patients had upper airway obstruction. Polysomnography was performed in 30 infants: 53.3% had obstructive and/or central apnoeas. Overall fatality rate was 10.4% and fatality due to upper airway obstruction was 2%.
van Lieshout et al, 2014 [45]	Retrospective, cohort study	IV	59 infants with Robin sequence born between 2000-2010 (49% females; age < 1 year)	61% of patients had isolated Robin sequence; 14% had syndromal Robin sequence (Treacher Collins syndrome, Stickler syndrome, Nager syndrome, Miller syndrome, Trisomy 19, chromosome 11 duplication-12 (q23,3:q24,3) deletion); 25% had associated abnormalities without a diagnosed syndrome (hypertelorism, microtia, etc.). Most patients underwent upper airway

				endoscopy and/or polysomnography. An obstructive AHI <1 episode/h was considered normal, 1-5 episodes/h mild OSAS, 5-24 episodes/h moderate OSAS, and >24 episodes/h severe OSAS. 42 of 59 (71.2%) subjects had one or more sleep studies: 7.1% of patients had mild OSAS; 7.1% had moderate OSAS; and 19% had severe OSAS. 12 of 42 children underwent upper airway endoscopy: in 6 of 12 patients the tongue base was placed against the posterior pharyngeal wall. 69.5% of 59 children were managed with prone positioning only; 10.2% initially were placed in the prone position but subsequently required oxygen administration, nasopharyngeal airway insertion, CPAP or mandibular distraction

				osteogenesis (1 case). 4 of 59 (6.8%) patients required endotracheal intubation in the neonatal period which was followed by tracheostomy and in one case the tracheostomy was followed by mandibular distraction osteogenesis. The remaining 8 patients were managed by intubation (one case), oxygen administration, nasopharyngeal airway insertion or CPAP followed in 4 cases by mandibular distraction osteogenesis. 47% of infants were supported by nasogastric or gastrostomy tube feedings. 3 (5%) patients died.
Daniel et al, 2013 [46]	Retrospective case series	IV	39 infants with Pierre Robin sequence (age 5-141 days) of which 17 had an associated cleft palate.	Of 39 infants studied, 10 (25.6%) had mild/moderate OSAS (AHI 1-10 episodes/h), and 29 (74.4%) severe

				OSAS (AHI >10 episodes/h). Infants with severe OSAS required more airway interventions while in hospital (82.8% vs. 30.0%; P = 0.004) and at discharge (72.4% vs. 20.0%; P = 0.007) than those with mild/moderate OSAS. More specifically, 30% of infants with mild/moderate OSAS required CPAP while in the hospital and 20% on discharge. In comparison, amongst those with severe OSAS, 82.8% required airway interventions while hospitalised: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required CPAP on discharge. Those with severe OSAS were more likely to require tube feedings on discharge (89.7 vs. 50%; P = 0.02). Children were on a lower weight centiles at discharge compared to

				birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles), irrespective of OSAS severity or need for airway interventions or tube feeding.
Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had an oximetry study between 2000 and 2010 (age 1 day to 12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score was 4. The presence of obstructive events and increased work of breathing were used to re-classify UAO severity if necessary. If UAO was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up

				sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were managed with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in 13.4% of cases.
Anderson et al, 2011 [48]	Cross-sectional study		IV	13 infants with Pierre Robin sequence who underwent polysomnography in the first year of life (11 girls; mean age 48 days; range: 7-214 days).	OSAS was diagnosed in 11 of 13 (85%) infants. Mean obstructive AHI was 33.5 episodes/h (range: 0-85.7 episodes/h). OSAS was of mild severity in 18% of patients, moderate in 27% and severe in 55%. An elevated mean end-tidal PCO_2 of 59 mmHg (range: 47-76 mmHg) was identified. Mean SpO_2 nadir was 80% (range:

				68%-93%). Snoring was present in only 7 of 13 (54%).
Cheng et al, 2011 [49]	Case series	IV	6 infants who failed treatment with CPAP out of 20 infants with Pierre Robin sequence and respiratory distress.	The follow-up interval was 9 months to 6 years. All infants underwent laryngoscopy and bronchoscopy under general anesthesia which revealed glossoptosis resulting in near-complete upper airway obstruction while in the prone position. Additional obstructive lesions were found: unilateral choanal atresia, hypoplastic epiglottis, laryngomalacia, tracheal stenosis. Preoperative polysomnography demonstrated an average respiratory disturbance index >27 episodes/h. Maximum CO_2 was 56-85 mmHg. Mandibulotomy, insertion of resorbable distractors and glossopexy

					were performed between 26 days and 11 months of age. Serial polysomnography studies were carried out postoperatively. Average respiratory disturbance index decreased to 7.3 episodes/h and maximum CO_2 to 34-45 mmHg. Weight percentile increased.
Schaefer et al, 2004 [50]	Retrospective, cohort study		IV	21 patients with isolated Pierre Robin sequence treated by one surgeon over a 9-year period; 18 of 21 infants presented during the first week of life; 3 other infants were 12-33 months old.	Patients were followed for a median period of 33 months (range 9-70 months). Airway patency was achieved with prone positioning for 10 patients, with tongue-lip adhesion for 7 of 10 patients who underwent the procedure, with tracheostomy for 2 patients, and with mandibular distraction osteogenesis for 3 patients. There was significant change in the maxillary-mandibular discrepancy

				during the first year of life (P <0.0001). Oromotor studies performed ≥3 months after reversal of tongue-lip adhesion reversal (n = 9) demonstrated no deficits in tongue function, relative to other children with cleft lips/palates.
Sher et al, 1992 [51]	Retrospective, cohort study		IV	53 infants with Robin sequence aged 1 day to 9 months.	All infants underwent nasopharyngoscopy and type of obstruction was classified according to Sher et al, 1986: Type I obstruction in 58.5% of infants; type II in 20.8%; type III in 9.4%; and type IV in 9.4% of infants.
Sher et al, 1986 [52]	Retrospective, cohort study		IV	33 patients with craniofacial abnormalities and upper airway obstruction with ages 0 to 24 years.	Patients underwent polysomnography, nasopharyngoscopy and cephalometry. Obstruction at the oropharyngeal level was classified in 4 categories: posterior

				movement of the tongue towards the posterior pharyngeal wall; compression of the soft palate on the posterior pharyngeal wall by the tongue; collapse of the lateral pharyngeal walls; circular constriction of the pharynx. Nasopharyngeal tube, glossopexy, mandibular advancement or tracheostomy were selected based on endoscopic findings.
f. *Neuromuscular disorders (cerebral palsy, mitochondrial disorders, spinal muscular atrophy)*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Mosquera et al, 2014 [53]	Retrospective, cohort study	IV	18 children with mitochondrial disorder aged 1.5-18 years (5 of 18 ≤2 years old); mostly non-obese	All children underwent polysomnography; SDB defined as: presence of OSAS (obstructive AHI > 1 episode/h); central sleep apnoea; hypoxaemia (SpO_2 <90% for >2% of total sleep time); or hypoventilation. SDB was present in 56% of the subjects. The most

				common type of SDB was OSAS (diagnosed in 6/18 subjects with a mean AHI of 2.7 episodes/h).
Verrillo et al, 2014 [54]	Retrospective, cohort study	III	12 infants with spinal muscular atrophy-type 1 (mean age 5.9 months), 10 controls (mean age 4.8 months)	Patients and control infants underwent polysomnography. Infants with spinal muscular atrophy had increased sleep latency and a higher AHI compared to controls (4.77 ± 3.59 episodes/h vs 0.68 ± 0.46 episodes/h).
Testa et al, 2005 [55]	Cross-sectional study	IV	14 infants with spinal muscular atrophy 1 or 2, aged 11.7 ± 11.4 months and 28 controls aged 10.1± 8.9 months	Patients with spinal muscular atrophy had significantly higher AHI compared to controls (median 1.9 [0.4–4.6] episodes/h vs 0.3 [0–2.3] episodes/h). Thoracoabdominal asynchrony was present during the inspiratory and expiratory phases in both quiet and active sleep: phase angle in quiet sleep, phase angle in active

					sleep, phase relation during inspiration for a breath during active sleep and quiet sleep, phase relation during expiration for a breath during active sleep and quiet sleep were all significantly greater than that demonstrated in control participants.
Kotagal et al, 1994 [56]	Retrospective, cohort study	III		9 children with severe cerebral palsy (spastic quadriparesis, severe psychomotor retardation, seizures) aged 7 months-10.4 years, who had nosiy breathing and disturbed night sleep; 9 control subjects with history of recurrent apnoea and/or enuresis aged 11 months-10.5 years.	All children underwent polysomnography. Obstructive hypopneas were defined as respiratory events with a decrease in oral-nasal airflow signal amplitude $\geq$50% and SpO_2 drop $\geq$3%. Respiratory disturbance index was defined as the number of apnoeas and hypopneas per hour of sleep. The mean respiratory disturbance index was 5.39 episodes/h (0.81-10.07 episodes/h) in children with cerebral palsy and 2.16 episodes/h (0-5.4

				episodes/h) in controls (P<0.01). 4 children with cerebral palsy had OSAS related to adenotonsillar hypertrophy and underwent adenoidectomy or adenotonsillectomy and 1 had OSAS related to micrognathia and tracheal stenosis and was treated with tracheostomy.

g. *Complex abmormalities (achondroplasia, Beckwith-Wiedemann syndrome, Chiari malformation, Down syndrome, mucopolysaccharidoses, Prader-Willi syndrome)*

Author, year	Type of Study	Class	Subjects	Methods and findings
Achondroplasia				
Ednick et al, 2009 [57]	Retrospective, cohort study	III	12 infants with achondroplasia and 12 aged-matched control infants	Polysomnographic records for both patients and controls were reviewed. Brain MRIs in infants with achondroplasia were also reviewed to evaluate the size of the foramen magnum and assess its relationship to SDB. Infants with achondroplasia had a significant increase in total respiratory disturbance

				index (13.9 ±10.8 episodes/h in the achondroplasia group versus 2.0 ± 0.9 episodes/h in the control group; P <0.05). However, there were no significant differences in percentages of active sleep, quiet sleep, or sleep efficiency. Infants with achondroplasia had decreased spontaneous arousal index (10.5 ±3.5 episodes/h in the achondroplasia group versus 18.6 ± 2.7 episodes/h in controls; P <0.0001) and respiratory arousals (10.3% ± 6.3% in infants with achondroplasia group versus 27.5% ± 9.5% in the control group; P < .0001). There were no significant correlations between the anteroposterior or transverse diameters and RDI.

Beckwith-Wiedemann syndrome				
Kamata et al, 2005 [58]	Case report	-	2 infants with Beckwith-Wiedemann syndrome who developed OSAS after 1-stage repair for omphalocele.	CASE 1: Obstructive apnoea index was17.3 episodes/h, and SpO2 was lower than 95% for 80% of the total sleep time. CT and MRI revealed obstruction of the upper airway between the large tongue and the hypopharynx. Central tongue resection and division of the frenulum linguae for associated ankyloglossia were performed 97 days after birth. One month postoperatively, apneic events resolved and SpO_2 was below 95% for only 1% of the total sleep time. CASE 2: Obstructive apnoea index was 28.1 episodes/h. Division of the frenulum linguae and anterior glossopexy were carried out 55 days after birth. Postoperative polysomnogram indicated

				a marked reduction in the obstructive apnoea index.
Chiari malformation				
Khatwa et al, 2013 [59]	Retrospective, cohort study	IV	22 children with Chiari malformation type I (11 males; median age 10 years, range 1-18 years)	3 children had central sleep apnoea, 5 had OSAS and one child had both obstructive and central sleep apnoeas. Children with SDB had excessive crowding of the brainstem structures at the foramen magnum and greater length of herniation relative to children without SDB. Patients with central sleep apnoeas underwent surgical decompression, with improvement in polysomnography.
Alsaadi et al, 2012 [60]	Retrospective, cohort study	IV	16 children (11 boys; mean age 4.7 years; range, 0.8-10 years) with Chiari II malformation	Overnight polysomnography was performed. Mean AHI was 6.3 episodes/h (range 0.2-24.5 episodes/h). The mean central apnoea-hypopnoea index was 5.9 episodes/h (range 0-24.5

				episodes/h) and the mean obstructive AHI was 0.4 episodes/h (range 0-2.9 episodes/h).
Down syndrome				
Goffinski et al, 2015 [61]	Retrospective, cohort study	IV	177 infants with Down syndrome	59 patients underwent polysomnography due to clinical concerns. 95% of infants had OSAS (AHI ≥2 episodes/h) and 71% of them had severe disease (AHI ≥10 episodes/h). The minimum overall prevalence of OSAS among the larger group of infants was 31% (56/177).
Lin et al, 2014 [62]	Retrospective, cohort study	III	49 children with Down syndrome referred for polysomnography; 49 otherwise healthy children suspected for OSAS matched for gender, age, and SDB severity who underwent polysomnography during the same period (46 females; mean age of all	Parents completed a SDB symptom questionnaire. Children with Down syndrome had median obstructive AHI 6.1 episodes/h (range 0-38 episodes/h) and control subjects 6.5 episodes/h (range 0-30 episodes/h) (P = 0.87). Children with Down syndrome had more

			participants 6.2 years (range 0.3-16.9 years); a cohort of 278 typically developed children referred for polysomnography was also included for comparison.	severe OSAS compared to 278 typically developing children (P<0.001). Symptom scores were not different between the matched groups. Severe OSAS was diagnosed in 8 of 18 children with Down syndrome aged < 3 years (44%). Participants with Down syndrome had higher average pCO_2 during sleep (P = 0.02) and worse McGill oximetry scores.
Shott et al, 2006 [63]	Prospective, cohort study	IV	56 children with Down syndrome over a 5-year period	Children underwent polysomnography at a mean age of 42 months (4-63 months). A questionnaire on sleep patterns was completed by parents. Abnormal polysomnography was defined as obstructive index >1 episode/h or carbon dioxide level >45 mm Hg for >2/3 of the study or >50 mm Hg for

				>10% of the study, and/or unexpected SpO_2 <92% during sleep or repeated intermittent desaturations <90%. 57% of children had OSAS but of the parents who reported abnormal sleep patterns only 36% had abnormal polysomnography.
Stebbens et al, 1991 [64]	Retrospective, cohort study	IV	32 children with Down syndrome (median age 1.4 years; range 0.1-4.9 years)	Parental questionnaires were completed and chest wall movements and SpO_2 were recorded. Children with Down syndrome had increased frequency of stridor and chest wall retractions during sleep, reduced baseline SpO_2, increased frequency of $SpO_2 \leq 90\%$ in the presence of chest wall movements.
Mucopolysaccharidoses				
Pal et al, 2015 [65]	Retrospective, cohort study	IV	61 children with type I mucopolysaccharidosis (44 Hurler phenotype, 17	A total of 150 sleep oximetry studies were analysed. SDB was

			attenuated cases) who underwent nocturnal oximetry between 6 months pre- to 16 years post-treatment (median follow-up 22 months).	defined as ODI 4% > 5 episodes/h and median SpO_2 <95%. Moderate SDB was diagnosed if ODI4% was 5–10 episodes/h and severe SDB as ODI4% >10 episodes/h. The incidence of SDB was 68% and 16% of participants required therapeutic intervention for airway obstruction. Greater frequency of SDB progression and requirement for treatment intervention were demonstrated amongst patients under enzyme replacement therapy as compared to those who underwent haematopoietic stem cell transplantation.
Nashed et al, 2009 [66]	Retrospective, cohort study	IV	14 patients with mucopolysaccharidosis (median age 5.2 years; range 0.8-17.8 years) who underwent polysomnography	The obstructive AHI was 6.6 episodes/h (0.0-54.8 episodes/h) and the central apnoea index was 0.6 episodes/h (0.0-2.6 episodes/h). Seven of 11

				(64%) participants had OSAS and 3 of them had severe OSAS (obstructive AHI >10 episodes/h); 5 of 7 children underwent treatment for OSAS and in 3 of 5 treated children, a reduction in obstructive AHI was demonstrated. Two patients with OSAS and on enzyme replacement therapy had also improvement in the obstructive AHI.
Prader-Willi syndrome				
Cohen et al, 2014 [67]	Retrospective, cohort study	IV	44 patients with Prader-Willi (0.3-15.6 years old; 23 subjects <2 years of age)	Children aged <2 years had more frequently central sleep apnoea compared to older children (43% vs. 5%; P = 0.003). Obstructive events were prevalent in older children. Supplemental oxygen was used in 9 infants with Prader-Willi syndrome and central sleep apnoea and the median central apnoea index decreased from 14 to 1 episode/h (P = 0.008).

| Sedky et al, 2014 [68] | Quantitative review | - | 14 studies of children with Prader-Willi syndrome and who underwent polysomnography in order to exclude OSAS (n = 224 children) | Prevalence of OSAS across studies was 79.91% (179/224); 53.07% had mild OSAS, 22.35% moderate OSAS, and 24.58% severe OSAS. The prevalence of OSAS was 88.89% (32/36) in patients aged ≤2 years, 88.89% (32/36) in the > 2 to ≤ 7-year age group, 86.49% (32/37) in the > 7 to ≤ 14-year age group, and 76.19% (16/21) in the > 14 to ≤ 18-year age group (P >0.05). Younger children and those with higher BMI z scores had higher AHI. Narcolepsy was present in 35.71% of cases. Adenotonsillectomy was associated with improvement in OSAS for most children but residual OSAS was present in the majority of cases postoperatively. |

1.4. What is the role of upper airway endoscopy and upper airway imaging in the evaluation of OSAS in young children?

a+b. *Indications and sedation for endoscopy*

Author, year	Type of Study	Class	Subjects	Methods and findings
Cheng et al, 2011 [49]	Case series	IV	6 infants who failed treatment with CPAP out of 20 infants with Pierre Robin sequence and respiratory distress.	The follow-up interval was 9 months to 6 years. All infants underwent laryngoscopy and bronchoscopy under general anesthesia which revealed glossoptosis resulting in near-complete upper airway obstruction while in the prone position. Additional obstructive lesions were found: unilateral choanal atresia, hypoplastic epiglottis, laryngomalacia, tracheal stenosis. Preoperative polysomnography demonstrated an average respiratory disturbance index >27 episodes/h. Maximum CO_2 was 56-85 mmHg. Mandibulotomy, insertion of resorbable

				distractors and glossopexy were performed between 26 days and 11 months of age. Serial polysomnography studies were carried out postoperatively. Average respiratory disturbance index decreased to 7.3 episodes/h and maximum CO_2 to 34-45 mmHg. Weight percentile increased.
Bravo et al, 2005 [69]	Retrospective, cohort study	IV	52 children with Pierre Robin sequence (median age 1 year and 7 months; range: 1 month-4 years; 29 female)	A questionnaire regarding children's sleeping habits and sleep symptoms was completed. Each patient had evaluation of craniofacial characteristics and upper airway patency, polysomnography and video nasopharyngoscopy. OSAS was diagnosed when the obstructive respiratory disturbance index was >5 episodes/h. Upper airway patency evaluated by endoscopy

				was classified as: no obstruction; mild obstruction; moderate obstruction; severe obstruction. OSAS was diagnosed in 31 of 52 children (59.6%). Moderate or severe obstruction on nasopharyngoscopy had 87% sensitivity and 100% specificity for the detection of OSAS.
Goldberg et al, 2005 [37]	Case series	IV	39 children with median age 15 months (range 1-126 months) who had OSAS (AHI ≥1 episode/h); 16 children ≤24 months; 17 patients were hypotonic and 22 had normal muscular tone	A flexible fiberoptic bronchoscope was used. Abnormalities were categorized in: fixed (narrow nostrils; adenoidal hypertrophy; tonsillar hypertrophy; tongue enlargement) and dynamic (inspiratory pharyngeal collapse at the glottis entrance; laryngomalacia). Most frequent fixed airway abnormalities were: adenoidal hypertrophy (64%) and

				tonsillar hypertrophy (31%). The reported dynamic abnormalities were: laryngomalacia (44%) and inspiratory pharyngeal wall collapse (38%). A large proportion of patients (41%) had both dynamic and fixed abnormalities.
Mitchell et al, 2003 [38]	Retrospective, cohort study	IV	23 children with Down syndrome aged 1 day to 10.2 years (median age: 6 months) referred for evaluation of upper airway obstruction 11 with polysomnography, no description of sleep parameters or AHI index	The most common diagnostic procedure was flexible laryngoscopy; 10 children had laryngomalacia and 1 child was diagnosed with tracheomalacia. Eight patients were evaluated by bronchoscopy and 4 of them had laryngomalacia and episodes of cyanosis. Eleven children had OSAS (48%), 8 of whom were >2 years old; 73% of children with OSAS had recurrent otitis media. Gastroesophageal reflux was a comorbidity in 14

				children (61%). Chronic lung disease was present in 13 children (56%), 6 of whom were preterm. Congenital heart disease was present in 11 children (48%) and pulmonary hypertension in 7 children (30%).
Sher et al, 1992 [51]	Retrospective, cohort study	IV	53 infants with Robin sequence aged 1 day to 9 months.	All infants underwent nasopharyngoscopy and type of obstruction was classified according to Sher et al, 1986: Type I obstruction in 58.5% of infants; type II in 20.8%; type III in 9.4%; and type IV in 9.4% of infants. 48 (90.6%) patients responded well to insertion of nasopharyngeal tube. 24 infants (all with type I obstruction) underwent glossopexy. 7 infants with pharyngeal obstruction types II-IV who did not respond to insertion of

				nasopharyngeal tube required tracheostomy.
Croft et al, 1990 [70]	Retrospective, cohort study	IV	15 infants and young children with documented OSAS	A flexible endoscope was used under light anesthesia. Sleep-endoscopy revealed the site of obstruction and guided treatment interventions.
Sher et al, 1986 [52]	Retrospective, cohort study	IV	33 patients with craniofacial abnormalities and upper airway obstruction with ages 0 to 24 years.	Patients underwent polysomnography, nasopharyngoscopy and cephalometry. Obstruction at the oropharyngeal level was classified in 4 categories: posterior movement of the tongue towards the posterior pharyngeal wall; compression of the soft palate on the posterior pharyngeal wall by the tongue; collapse of the lateral pharyngeal walls; circular constriction of the pharynx. Nasopharyngeal tube, glossopexy,

| | | | | mandibular advancement or tracheostomy were selected based on endoscopic findings. |
| | | | | |

c. *Upper airway imaging (CT or MRI scan)*

Author, year	Type of Study	Class	Subjects	Methods and findings
Paes et al, 2013 [71]	Systematic review		12 studies including 212 infants (<18 m.o.) with Robin sequence who underwent mandibular distraction osteogenesis.	82% of patients had isolated Robin sequence, 8% had Stickler's syndrome, 2% had Treacher Collins syndrome and 1% had Opitz syndrome. A cleft palate was present in 79% of cases. Upper airway endoscopy and polysomnography in combination with cephalometry and/or 3D CT scans was conducted in most patients. The mean age of initiating mandibular distraction osteogenesis varied from 8.3 to 9.6 weeks of age. The mean duration of the distraction process varied from 8.5 to 17 days.

				Tracheostomy was avoided or decannulation was achieved in 82% to 100% of patients.
Rachmiel et al, 2012 [72]	Prospective, cohort study	IV	11 children (4 months to 6 years old) with OSAS and micrognathia who were tracheostomy-dependent	Distraction osteogenesis was used to enlarge the airway and achieve decannulation. Bilateral distraction in the mandibular body was carried out using extraoral distraction devices. Three-dimensional computed tomography reconstruction of the face and neck before and after the intervention demonstrated mandibular elongation of a mean of 30 mm on each side, an increase in mandibular volume by an average of 29.19%, and increase in pharyngeal airway by an average of 70.53%. Two to 3 months following completion of the intervention, all 11 patients were decannulated

				with improvement in signs and symptoms of OSAS and no need for supplemental oxygen. Mean follow-up was 2.0 years. The respiratory disturbance index was <2 episodes/h for all patients.
Visvanathan et al, 2012 [73]	Case series		10 children who were diagnosed with nasal pyriform aperture stenosis	There were features of airway obstruction: persistent nasal congestion, tachypnoea, episodes of apnoea/cyanosis, poor feeding. Resistance was felt during passage of a nasogastric tube. All patients underwent craniofacial CT scan. 5 children were managed by nasal decongestants, humidification, nasopharyngeal airway insertion and management of laryngopharyngeal reflux. The remaining 5 patients who did not respond to conservative

				management (i.e. worsening oxygen desaturations, recurrent episodes of apnoea/cyanosis and failure to thrive) were treated surgically. All infants who underwent surgery had bilateral pyriform aperture stenosis. A sublabial approach was used and excess bone was drilled away from the inferior inlet along the floor of the nose to the lateral process of the maxilla. Surgery was performed at an average age of 14 days (range 3–26 days).
Looby et al, 2009 [74]	Retrospective, cohort study	IV	17 infants with syndromic or nonsyndromic micrognathia who underwent mandibular distraction osteogenesis at the average age of 105 days (range 11-310 days)	Surgery was performed if there was no response to conservative measures i.e. prone positioning or nasopharyngeal airway insertion. Failure of conservative treatment was defined as refractory

				apnoea, inadequate weight gain, or lack of parental compliance. Preoperative assessment included 3-dimensional CT of the head and neck, polysomnography, direct or fiberoptic laryngoscopy, modified barium swallow study and esophageal pH testing. These tests were repeated postoperatively. Preoperatively, the mean AHI was 10.6 episodes/h (range 0-43.1 episodes/h), and the mean SpO_2 nadir was 83% (range 66%-98%). Postoperatively, the mean AHI decreased to 2.2 episodes/h (range 0-12.9 episodes/h), and the mean SpO_2 nadir increased to 90% (range, 81%-98%). The mean retroglossal oropharyngeal cross-sectional area increased from 41.53 mm^2 to 127.77 mm^2.

Online Supplementary Table S2

Topic 2: Recognition of morbidity and conditions frequently co-existing with OSAS in young children

2.1. Does OSAS in young children increase the risk of pulmonary hypertension and cor pulmonale?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Tal et al, 1988 [75]	Retrospective, cohort study	IV	27 children (mean age 3.5 years; range: 9 months to 7.5 years) with oropharyngeal obstruction and clinical features of OSAS.	Radionuclide ventriculography was used to evaluate ventricular function before ± after adenotonsillectomy. Reduced right ventricular ejection fraction (<35%) was demonstrated in 10 (37%) patients: mean fraction 19.5% with SE 2.3% and range: 8-28%). Wall motion abnormality was found in 18 (66.7%). Radionuclide ventriculography was performed before and after adenotonsillectomy with improvement in wall motion and significant

				increase in right ventricular ejection fraction from 24.4% ± 3.6% to 46.7 ± 3.4% (P <0.005). In five children, left ventricular ejection fraction increased more than 10% postoperatively.
Levine et al, 1982 [76]	Case series		4 infants with Down syndrome and symptoms of OSAS	Clinical manifestations included noisy breathing, intercostal retraction, cyanosis, frequent apnoeas during sleep, and daytime lethargy and somnolence. Hypoventilation especially during sleep was demonstrated by arterial blood gas analyses. Inspiratory pharyngeal closure was detected by fluoroscopy in one infant. Partial improvement was achieved by adenoidectomy in one case and temporary improvement by adenotonsillectomy in 2 patients. Tracheostomy

				was required in 3 cases.
Cogswell et al, 1974 [77]	Case report		5-week-old infant with micrognathia, cleft palate, stridor, feeding difficulties and episodes of cyanosis	Clinical findings and ECG consistent with cor pulmonale. Biventricular hypertrophy was present. Persistent cyanosis was present and hypercapnia was detected in capillary blood samples. Airway resistance was measured in different postures. Transthoracic pressure swings were recorded with an esophageal balloon and airflow and tidal volume were recorded using a pneumotachograph placed on a face mask. In the prone position, tidal volume was maximized and esophageal pressure swings were minimized.

2.2. Do young children with OSAS have increased risk of delayed growth?

a. *Delayed growth is a complication of OSAS*

Author, year	Type of Study	Class	Subjects	Methods and findings
Nachalon et al, 2014 [78]	Prospective, cohort study	IV	20 children (6-36 months old) diagnosed with OSAS (obstructive AHI >5 episodes/h)	Children were evaluated before and 5 ± 2 months after adenotonsillectomy and height, weight, circulating high sensitive C-reactive protein (CRP), and insulin-like growth factor 1 (IGF-1) levels were measured. Caloric intake was assessed by a validated Short Food Frequency Questionnaire (SFFQ). Postoperatively, children had mean increase of 4.81 cm in height and 1.88 kg in weight ($P < 0.001$ for both) and a significant increase in BMI z-score ($P = 0.007$). Increased caloric intake (mean 377 kcal/day) was recorded ($P < 0.001$), with increased protein and decreased fat intake. Reduction in CRP levels correlated with the increase in body weight in boys ($P < 0.05$ after

				adjustment for caloric intake).
Freeman et al, 2012 [10]	Prospective, cohort study	IV	10,441 children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC) with SDB symptoms parental report by questionnaire at 6, 18, 30, 42, 57, 69, and 81 months of age.	Five clusters emerged from 10,441 children and were defined according to patterns of mean severity of SDB symptoms over the study period: "normals" (50%) who were asymptomatic; "late snores and mouth-breathing" cluster (20%) who remained asymptomatic until 4 years old; "early snores" (10%) and "early apnoea" (10%) clusters with peak symptoms at 6 and 18 months, respectively; the "all SDB after infancy" (10%) with symptoms which peaked from 30 to 42 months and remained elevated. Children belonging to the "early snores" cluster were significantly shorter than "normals".

b. *Younger children with OSAS have increased frequency of growth failure or delay compared to older children*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Czechowicz et al, 2015 [79]	Retrospective, cohort study	IV	76 children with laryngomalacia who underwent supraglottoplasty at age <2 years	Somatic growth changes from the time of surgery to an average of 9 months postoperatively were recorded. BMI increased from a mean of 15.4 kg/m^2 to 18.0 kg/m^2 and BMI percentile from a mean of 34th preoperatively to 51st postoperatively. The largest BMI percentile increases were recorded in infants that were 3 months old or younger at the time of supraglottoplasty, and in those under 12 months of age, who were in the lowest BMI quintile.

2.3. Does OSAS in young age affect behaviour and cognitive development?				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Smith et al, 2014 [80]	Retrospective, cohort study	IV	33 children who had polysomnography at the	At the age of 36.7 ±1.4 years, they underwent

				age of 2.7 ± 2.1 months for cleft lip and/or palate	neurocognitive (Bayley Scales of Infant and Toddler Development, Third Edition; BSID-III), quality of life (Infant/Toddler Quality of Life Questionnaire-ITQOL) assessments and evaluation of somatic growth. AHI in infancy was 23.9 ± 18.0 episodes/h and the obstructive AHI was13.5 ± 14.3 episodes/h. Mean group BSID-III scores were within the standardized normal range for all domains, but language scores were lower than normal. Quality of life scores and growth parameter z-scores were similar to published control data. Lower percentage of active/REM sleep in infancy was associated with lower cognition scores; higher obstructive AHI was related to lower global

				behavior ITQOL score; children with higher AHI in infancy had lower weight z-score compared to those with lower AHI.
Bonuck et al, 2012 [81]	Prospective, cohort study	I	n = 9140 at 4 years of age and n = 8098 at 7 years of age	Parents' report on children's snoring, mouth breathing, and witnessed apnoea at 6, 18, 30, 42, 57, and 69 months of age and completion of the Strengths and Difficulties Questionnaire at 4 and 7 years of age. The SDB clusters predicted approximately 20% to 100% increased odds of problematic behavior, after controlling for multiple potential confounders.
Piteo et al, 2011 [82]	Prospective, cohort study	III	13 children (10 males) with snoring shortly after birth which persisted ≥3 nights/week at the ages of 6 and 12 months; 78 healthy control infants (31	Infants were evaluated at the age of 6 and 12 months with the Bayley Scales of Infant and Toddler Development edition III; parents

				males) without snoring apart from colds	completed demographic, sleep, and developmental surveys. Cognitive development was reduced in infants with frequent snoring at 6 and 12 months of life (mean 94.2 ± 3.9) compared to control infants (mean 100.6 ± 3.7) (P <0.001).
Piteo et al, 2011 [83]	Prospective, cohort study	III	16 children (13 males) with snoring shortly after birth which persisted ≥3 nights/week at the age of 6 months; 88 healthy control infants (36 males) without snoring apart from colds	Infants were evaluated at the age of 6 months with the Bayley Scales of Infant and Toddler Development edition III; parents completed demographic, sleep, and developmental surveys. Cognitive development was reduced in infants with frequent snoring at the age of 6 months (mean 95.3; SD 4.3) compared to control infants (mean 100.6; SD 3.9) (P <0.01).
Montgomery-Downs et al, 2006 [84]	Cross-sectional study	IV	35 healthy infants from the community aged 8.2 ±	All infants were administered the Bayley

			0.4 months	Scales of Infant Development, including the Mental Development Index and underwent polysomnography. AHI for all participants was 0 episodes/h. Respiratory arousal index (snoring-associated arousals) was significantly correlated with the Mental Development Index. Spontaneous arousals and arousals associated with central apnoea and oxyhaemoglobin desaturation episodes (≥4%) were not significantly correlated with the index.

2.4. Which conditions frequently co-exist with OSAS (potential common pathogenetic mechanisms) and may improve with OSAS treatment?

a. *Feeding difficulties*

Author, year	Type of Study	Class	Subjects	Methods and findings
Durvasula et al, 2014 [85]	Retrospective, cohort	IV	28 infants (≤12 months)	Comparisons to 136

	study		and 26 children (>12 months) who underwent supraglottoplasty for severe laryngomalacia and were diagnosed with a neurologic condition (cerebral palsy, developmental delay, Chiari I malformation, hydrocephalus, Dandy-Walker malformation) or syndromic comorbidity (including CHARGE, VATER, Down syndrome and others).	infants without comorbidities who underwent supraglottoplasty were carried out. Overall success rate of supraglottoplasty in the study population with comorbidities was 67%. Neurologic conditions (P = 0.003) and syndromic comorbidities (P < 0.001) were associated with significantly reduced success rates when compared to no comorbidities. Among children with inadequate response to surgical treatment (18 of 54; 33%), 13% (7 of 54) required tracheostomy, 9% (5 of 54) needed CPAP (persistent OSAS), 7% (4 of 54) required a postoperative gastrostomy tube, and 4% (2 of 54) required revision of supraglottoplasty. Patients with cerebral palsy had

				significantly higher frequency of tracheostomy than those with other neurologic disorders (2 of 11 [18%] vs 0 of 20; P = 0.049). In infants, acute airway obstruction was the most common indication for supraglottoplasty in the groups with neurologic disorders or syndromic comorbidities (success rates, 69% and 67%, respectively). In children, OSAS was the most common indication for surgery in the groups with neurologic disorders or syndromic comorbidities (success rates, 78% and 50%, respectively). Eleven infants (85%) and 14 children (78%) had preoperative dysphagia. Aspiration was identified by a videofluoroscopic swallow study or functional endoscopic evaluation of swallow, preoperatively in 8 of 8

				infants (100%) and 6 of 14 children (43%) without gastrostomy tube. Five infants (38%) and 4 children (22%) presented preoperatively with a gastrostomy. In the majority of patients dysphagia resolved postoperatively.
Garritano et al., 2014 [86]	Retrospective, cohort study	IV	17 infants who underwent supraglottoplasty for laryngomalacia aged 1-91 months)	Feeding problems were part of the indication for supraglottoplasty in 47% of 17 patients with laryngomalacia and failure to thrive in 29.4% of cases. OSAS symptoms were present in 29.4% of patients.
Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Pierre Robin sequence (age 5-141 days) of which 17 had an associated cleft palate.	Of 39 infants studied, 10 (25.6%) had mild/moderate OSAS (AHI 1-10 episodes/h), and 29 (74.4%) severe OSAS (AHI >10 episodes/h). Infants with severe OSAS required

				more airway interventions while in hospital (82.8% vs. 30.0%; P = 0.004) and at discharge (72.4% vs. 20.0%; P = 0.007) than those with mild/moderate OSAS. More specifically, 30% of infants with mild/moderate OSAS required CPAP while hospitalised and 20% on discharge. In comparison, amongst those with severe OSAS, 82.8% required airway interventions while hospitalised: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required CPAP on discharge. Those with severe OSAS were more likely to require tube feedings on discharge (89.7 vs. 50%; P = 0.02). Children were on a lower weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8

				centiles), irrespective of OSAS severity or need for airway interventions or tube feeding.
Greenfeld et al, 2003 [15]	Prospective, cohort study	IV	29 consecutive infants <18 months of age who underwent polysomnography and were diagnosed with OSAS due to adenotonsillar hypertrophy	A paediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of OSAS symptoms post-treatment was collected. Two infants underwent adenoidectomy only and the rest of them had adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants. Other symptoms included: sleep apnoea (72%), frequent movements

				during sleep (69%), mouth breathing (62%) and recurrent awakenings (38%); approximately 15% of infants had eating difficulties. Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$ percentile to the $42^{nd} \pm 32^{nd}$ percentile (P<0.001). 14/29 (48%) of the infants dropped two or more major percentiles prior to surgery. Following surgery, significant weight gain with an increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P<0.0001). 5/29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3/5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was

				documented in 6/23 (26%) of infants and repeat adenoidectomy was required.

b. *Recurrent otitis media*

Author, year	Type of Study	Class	Subjects	Methods and findings
Robison et al., 2012 [87]	Retrospective, cohort study	IV	295 infants (3-24 months old) diagnosed with OSAS (AHI >1.5 episodes/h)	94 (31.9%) infants had concomitant eustachian tube dysfunction which is increased compared to the prevalence of 4% to 7% in the general paediatric population. A total of 135 myringotomy + tympanostomy tube placement procedures were performed; 30 (31.9%) patients had two or more procedures. There was no difference in average age of first myringotomy + tympanostomy tube placement when the subgroups with mild, moderate, and severe OSAS were compared.
Mitchell et al, 2003 [38]	Retrospective, cohort	IV	23 children with Down	The most common

	study		syndrome aged 1 day–10.2 years (median age: 6 months) referred for evaluation of upper airway obstruction 11 with PSG, no description of sleep parameters or AHI index	diagnostic procedure was flexible laryngoscopy; 10 children had laryngomalacia and 1 child was diagnosed with tracheomalacia. Eight patients were evaluated by bronchoscopy and 4 of them had laryngomalacia and episodes of cyanosis. Eleven children had OSAS (48%), 8 of whom were >2 years old; 73% of children with OSAS had recurrent otitis media. Gastroesophageal reflux was a comorbidity in 14 children (61%). Chronic lung disease was present in 13 children (56%), 6 of whom were preterm. Congenital heart disease was present in 11 children (48%) and pulmonary hypertension in 7 children (30%).

Topic 3: Objective diagnosis and assessment of OSAS severity

Online Supplementary Table S3

3.1. What are the objective tools for the diagnosis of OSAS in young children?				
a+b. *Video polysomnography + polysomnography + nap polysomnography*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. The average age at follow-up was 7.7 ± 7 months.	Risk factors for OSAS among the studied infants Included: hypotonia (53%); gastroesophageal reflux (30%); laryngomalacia (24%); Down syndrome (19%); craniofacial abnormalities (16.5%); adenotonsillar hypertrophy (3%); epilepsy (5%); neuromuscular disease (2%); genetic abnormalities other than Down syndrome (34%). 40 (41%) infants had mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h).
Daniel et al, 2013 [46]	Retrospective, cohort	IV	39 infants with Robin	10 (25.6%) infants had

	study		sequence (age 5 to 141 days)	mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients or 74.4%) had severe OSAS (AHI >10 episodes/h). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge. 30.0% of infants with mild/moderate OSAS were placed on CPAP during admission and 20.0% of infants at discharge. Amongst those with severe OSAS, 82.8% required airway interventions: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge. Infants with severe OSAS required tube feeding at discharge more frequently than infants with

				mild/moderate OSAS (89.7% vs 50.0%). Children were at lower weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was repeated within 3–6

				months. OSAS was defined as obstructive AHI ≥ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI ≥25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without midface hypoplasia. Obstructive AHI

				decreased significantly over the first 3 years of life.
Kahlke et al, 2013 [88]	Retrospective, cohort study	IV	105 children aged 0-24 months who underwent polysomnography	SDB was defined as AHI $\geq$ 1.5 episodes/h and OSAS as an obstructive AHI $\geq$1.5 episodes/h and obstructive AHI. Polysomnography results from the first 4-h were compared to the full-length studies. Outcomes included total, obstructive, and central apnoea indices. Cut-off values for central apnoeas were 3 episodes/h for subjects >6 months old and 10 episodes/h for subjects $\leq$6 months old 104 children had SDB based on full-night polysomnography and 105 subjects had at least one REM period in the first 4 h of sleep. Mean SpO_2 and end-tidal pCO_2, did not significantly differ between full-night and 4-h

				polysomnography. 4-h polysomnography had high sensitivity for AHI (100% for ≤6 months old and 92.9% for >6 months old), obstructive AHI (97.9% and 91.1%, respectively), and central apnea index (100% and 72.2% respectively). Agreement was lower for those patients with lower AHI.
Leonardis et al., 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for

				moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40 patients had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS. 68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%),

				observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy (7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration and blood transfusion in cases of prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-

				intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale). Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%).
Ng et al, 2013 [90]	Review		-	10 of 147 articles included children aged less than 1 year without known major anomalies (e.g., Down syndrome) who were born at term after a normal gestation, without history	For obstructive apnoeas, the upper limit of normal values was <1 episode/h; similarly, for mixed apnoeas, the upper limit of normal values was <1 episode/h. For central

			of ALTEs or family history of sleep apnoea, SIDS, or ALTEs.	apnoea defined as cessation of respiratory effort for ≥3 seconds, the upper limit of normal was 45 episodes/h for 1-month-old infants, 30 episodes/h for 2-month-old infants, 22 episodes/h for 3-month-old infants, and between 10 and 20 episodes/h for the older age groups.
Marcus et al, 1991 [91]	Retrospective, cohort study	IV	53 patients with Down syndrome (mean age 7.4 ± 1.2 [SE] years; range 2 weeks to 51 years).	Chest wall movement, heart rate, electrooculogram, end-tidal pO_2 and pCO_2, transcutaneous pO_2 and pCO_2, and SpO_2 were recorded as part of daytime nap polysomnography. Sixteen patients had also overnight PSG. Nap polysomnograms were abnormal in 77% of children: 45% had OSAS, 4% had central sleep apnoeas, and 6% had

115

				mixed apnoeas; 66% had hypoventilation (end-tidal $pCO_2 >45$ mm Hg) and 32% hypoxaemia (SpO_2 <90%). Overnight PSGs were abnormal in 100% of children, with OSAS in 63% of patients, hypoventilation in 81%, and hypoxaemia in 56% of cases. Nap studies significantly underestimated the presence of abnormalities when compared to overnight PSGs. There were no clinical indications of OSAS in 36 (68%) children. Age, obesity and presence of congenital heart disease were not predictors of OSAS, hypoxaemia, or hypoventilation. Polysomnograms improved in all 8 children who underwent adenotonsillectomy, but they normalized in only 3 subjects.

c. *Polygraphy*

Author, year	Type of Study	Class	Subjects	Methods and findings
Pavone et al, 2015 [92]	Retrospective, cohort study	IV	82 patients with Prader-Willi syndrome, median age of 5.1 years (range 0.3-44.3), who were followed in three centers (France, Italy); 34 children were younger than 2 years	Overnight sleep polygraphy was performed and included recordings of: nasal pressure by nasal canula, thoraco-abdominal movements, tracheal sounds, body position, SpO_2 and heart rate. Hypopnoea was defined as a decrease in nasal airflow of at least 50% with a decrease in SpO_2 of at least 3 or 4% and/or an arousal. Central apnoea was scored in the absence of airflow with the cessation of respiratory effort, lasting > 20 sec or of shorter duration and associated with bradycardia and 3% or 4% haemoglobin oxygen desaturation. AHI was calculated as the sum of apnoeas and hypopnoeas per hour of

				total sleep time. SDB was defined as an AHI ≥ 1.5 events/h in children and ≥ 5 events/h in adults. SDB frequency was 53% in children and 41% in adults. The median central apnoea index was 0.1 events/h. Median values of minimum and mean SpO_2 were 88% and 97%, respectively. Sixty-three percent of patients had a minimum SpO2 <90%. The median desaturation index was 2 events/h.
Brockmann et al, 2013 [93]	Prospective, cohort study	III	37 healthy infants aged 1 month (22 boys)	Polygraphies (chest and abdominal wall movements, nasal pressure transducer, snoring, pulse oximetry, electrocardiogram) were performed at the age of 1 month and 3 months. At the age of 1 month, the median (minimum–maximum) central, obstructive, and mixed

				apnoea indices were 5.5 (0.9–44.3), 0.8 (0.1–6.7), and 0.3 (0–1.2) episodes/h, respectively. At the age of 3 months central, obstructive and mixed apnoea indices were 4.1 (1.2–27.3), 0.8 (0–2.3), and 0.1 (0–0.8) episodes/h, respectively. Mixed obstructive apnoea–hypopnoea index was 1.5 (0.2–7.0) episodes/h and 0.9 (0.2–4.4) episodes/h at the age of 1 and 3 months, respectively (P = 0.017). 1.2% of central apnoeas lasted >20 s. Periodic breathing was present in more than 90% of studied subjects.
Stebbens et al, 1991 [64]	Retrospective, cohort study	IV	32 children with Down syndrome (median age 1.4 years; range 0.1-4.9 years)	Parental questionnaires were completed and chest wall movements and SpO_2 were recorded. Children with Down syndrome had increased frequency of

				stridor and chest wall retractions during sleep, reduced baseline SpO_2, increased frequency of $SpO_2 \le 90\%$ in the presence of chest wall movements.
d. *Nocturnal pulse oximetry*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Pal et al, 2015 [65]	Retrospective, cohort study	IV	61 children with type I mucopolysaccharidosis (44 Hurler phenotype, 17 attenuated cases) who underwent nocturnal oximetry between 6 months pre- to 16 years post-treatment (median follow-up 22 months).	A total of 150 sleep oximetry studies were analysed. SDB was defined as ODI 4% > 5 episodes/h and median SpO_2 <95%. Moderate SDB was diagnosed if ODI4% was 5–10 episodes/h and severe SDB as ODI4% >10 episodes/h. The incidence of SDB was 68% and 16% of participants required therapeutic intervention for airway obstruction. Greater frequency of SDB progression and requirement for treatment intervention were

				demonstrated amongst patients under enzyme replacement therapy as compared to those who underwent haematopoietic stem cell transplantation.
Coverstone et al, 2014 [94]	Retrospective, cohort study	IV	119 consecutive children with trisomy 21 (median age 6 years; range 3 months-21 years) who underwent polysomnography for suspected obstructive SDB.	A McGill oximetry score of 1-4 was calculated from the oximetry recording of polysomnography by scorers blinded to the polysomnography result and each child's clinical course. Median AHI was 4.6 episodes/h (range 0-101.8 episodes/h), median obstructive AHI was 2.5 episodes/h (range 0-101.1 episodes/h) and median central apnoea index was 1.1 episodes/h (0-35.2 episodes/h). 50% of patients had obstructive AHI $\geq$2.5 episodes/h. 49.6% of children had a McGill Score of 1 (inconclusive); their median obstructive AHI

				was 1.0 episode/h (interquartile range 0.4-3.3 episodes/h). McGill score was 2 in 36.1% of patients; their median obstructive AHI was 4.5 episodes/h (interquartile range 1.3-8.8 episodes/h). In 14.3% of patients, the McGill score was 3 or 4; the median AHI was 16.1 episodes/h (interquartile range 9.3-45.5 episodes/h). In 10% of patients the central apnoea index was ≥2.5 episodes/h although obstructive AHI was <2.5 episodes/h) and 41.2% of them had McGill score of 2.
Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score

			4 weeks old when referred for evaluation.	was 4. The presence of obstructive events and increased work of breathing were used to re-classify UAO severity if necessary. If UAO was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were managed with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in 13.4% of cases.

Brouillette et al, 2000 [95]	Cross-sectional study	III	349 children (6 m.o.-18 y.o.) who were referred for polysomnography due to suspected OSAS.	Children underwent polysomnography including nocturnal oximetry with a mean sleep time of 8.1 ± 1.4 hours. OSAS was defined as a mixed/obstructive apnea/hypopnea index ≥ 1 episode/h. Oximetry was considered positive for OSAS if there were 3 or more clusters of desaturations (≥5 desaturations ≥4% within 10-30 min) and ≥3 desaturations to <90%. Of the 93 oximetry recordings read as positive, polysomnography confirmed OSAS in 90 patients (97% positive predictive value). However, children with a negative or inconclusive oximetry had 47% probability of having OSAS.

3.2. What are the cut-off values for the parametres of objective tools for the diagnosis of OSAS in young children?

a. *Reference values in healthy young children*

Author, year	Type of Study	Class	Subjects	Methods and findings
Duenas-Meza et al, 2015 [96]	Prospective, cohort study	IV	122 healthy infants (56% female) aged 1 to 18 months born and residing at high altitude (Bogota, Colombia: 2,640 m)	Overnight polysomnography was carried out. Four age groups were defined: group 1: < 45 days old; group 2: 3 to 4 months old; group 3: 6 to 7 months old; and group 4: 10 to 18 months old. Of 122 children enrolled, 50 had three consecutive polysomnographies and were analysed as a longitudinal subcohort. The following numbers of sleep studies were performed: group 1, 106 studies; group 2, 89 studies; group 3, 61 studies; and group 4, 25 studies. Apnoea-hypopnoea indices (total, central, and obstructive)

				were highest in group 1 (21.4, 12.4, and 6.8 episodes/h/, respectively) and decreased with age ($P < 0.001$). Mean SpO_2 during waking and sleep increased with age ($P < 0.001$). Nadir SpO_2 values during respiratory events were lower in younger infants. Longitudinal assessments of 50 infants confirmed the trends described for the cross-sectional dataset.
Brockmann et al, 2013 [93]	Prospective, cohort study	III	37 healthy infants aged 1 month (22 boys)	Polygraphies (chest and abdominal wall movements, nasal pressure transducer, snoring, pulse oximetry, electrocardiogram) were performed at the age of 1 month and 3 months. At the age of 1 month, the median (minimum–maximum) central, obstructive, and mixed apnoea indices were 5.5

				(0.9–44.3), 0.8 (0.1–6.7), and 0.3 (0–1.2) episodes/h, respectively. At the age of 3 months central, obstructive and mixed apnoea indices were 4.1 (1.2–27.3), 0.8 (0–2.3), and 0.1 (0–0.8) episodes/h, respectively. Mixed obstructive apnoea–hypopnoea index was 1.5 (0.2–7.0) episodes/h and 0.9 (0.2–4.4) episodes/h at the age of 1 and 3 months, respectively (P = 0.017). 1.2% of central apnoeas lasted >20 s. Periodic breathing was present in more than 90% of subjects studied.
Ng et al, 2013 [90]	Review	-	10 of 147 articles included children aged less than 1 year without known major anomalies (e.g., Down syndrome) who were born at term after a normal gestation, without history	For obstructive apnoeas, the upper limit of normal values was <1 episode/h; similarly, for mixed apnoeas, the upper limit of normal values was <1 episode/h. For central

			of ALTEs or family history of sleep apnoea, SIDS, or ALTEs.	apnoea defined as cessation of respiratory effort for ≥3 seconds, the upper limit of normal was 45 episodes/h for 1-month-old infants, 30 episodes/h for 2-month-old infants, 22 episodes/h for 3-month-old infants, and between 10 and 20 episodes/h for the older age groups.
Scholle et al, 2011 [97]	Cross-sectional study	III	209 healthy German children (1-18 y.o.)	One-night polysomnography was performed in 16 laboratories. Normative values of cardiorespiratory parameters were summarised. No obstructive and mixed apneas were identified Hypopnoeas and central apnoeas (≥20 sec) were infrequent. In addition, oxygen desaturations or arousals accompanying central apnoeas were rare.

b. *Frequency of central apnoeas*				
Author, year	**Type of Study**	**Class**	**Subjects**	
Ng et al, 2013 [90]	Review	-	10 of 147 articles included children aged less than 1 year without known major anomalies (e.g., Down syndrome) who were born at term after a normal gestation, without history of ALTEs or family history of sleep apnoea, SIDS, or ALTEs.	For obstructive apnoeas, the upper limit of normal values was <1 episode/h; similarly, for mixed apnoeas, the upper limit of normal values was <1 episode/h. For central apnoea defined as cessation of respiratory effort for ≥3 seconds, the upper limit of normal was 45 episodes/h for 1-month-old infants, 30 episodes/h for 2-month-old infants, 22 episodes/h for 3-month-old infants, and between 10 and 20 episodes/h for the older age groups.
Scholle et al, 2011 [97]	Cross-sectional study	III	209 healthy German children (1-18 y.o.)	One-night polysomnography was performed in 16 laboratories. Normative values of cardiorespiratory parameters were summarised. No

| | | | | obstructive and mixed apneas were identified Hypopnoeas and central apnoeas (≥20 sec) were infrequent. In addition, oxygen desaturations or arousals accompanying central apnoeas were rare. |

c. *Classification of OSAS severity*

Author, year	Type of Study	Class	Subjects	Methods and findings
Cote et al, 2015 [98]	Retrospective, cohort study	IV	Review of 9038 tonsillectomies performed over 7 years; 215 (2.4%) were carried out on children ≤2 years old; 74 of 215 underwent tonsillectomy for OSAS and 123 of 215 for SDB. Median age was 21 months (10–24 months); 2.5% of patients were <12 months old and 78.7% were >18 months old.	Diagnosis of SDB was based on clinical evaluation; OSAS was diagnosed with an obstructive AHI >1.5 episodes/h; children underwent urgent tonsillectomy without polysomnography after hospital admission for obstructive breathing patterns, oxygen desaturations and enlarged tonsils. Severe OSAS was defined as an obstructive AHI >10 episodes/h. 4.7% of tonsillectomies were performed due to previous

				hospitalisation for upper airway obstruction with hypertrophic tonsisls. Study data were compared with available Colorado data for each variable. The proportions of male, African-American, Hispanic, obese, underweight, premature, syndromic and daycare subjects in the cohort were significantly different than in the Colorado population. In multivariable analysis, African-Americans were at 12.5 times greater risk for having severe OSAS than Caucasians. Children with syndromes or craniofacial anomalies had 11 times greater risk ($P < 0.0001$), and patients in daycare had 2.2 times lower probability ($P=0.04$) of undergoing polysomnography before tonsillectomy. Weight did not influence requests for

				polysomnography.
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. The average age at follow-up was 7.7 ± 7 months.	Risk factors for OSAS among the studied infants Included: hypotonia (53%); gastroesophageal reflux (30%); laryngomalacia (24%); Down syndrome (19%); craniofacial abnormalities (16.5%); adenotonsillar hypertrophy (3%); epilepsy (5%); neuromuscular disease (2%); genetic abnormalities other than Down syndrome (34%). 40 (41%) infants had mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h).
Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Robin sequence (1 y.o.)	10 (25.6%) infants had mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients

				or 74.4%) had severe OSAS (AHI >10 episodes/h). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge. 30.0% of infants with mild/moderate OSAS were placed on CPAP during admission and 20.0% of infants at discharge. Amongst those with severe OSAS, 82.8% required airway interventions: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge. Infants with severe OSAS required tube feeding at discharge more frequently than infants with mild/moderate OSAS (89.7% vs 50.0%). Children were at lower

				weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was repeated within 3–6 months. OSAS was defined as obstructive AHI ≥ 1

				episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI ≥25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. Treatment for OSAS was offered at a median age of 4.5 years (range 4 months-18 years old). A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without

				midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.
Leonardis et al., 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥ 1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥ 15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40 patients

				had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS. 68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy

				(7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration and blood transfusion in cases of prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale).

				Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%).
d. *Classification of OSAS severity based on nocturnal oximetry*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Pal et al, 2015 [65]	Retrospective, cohort study	IV	61 children with type I mucopolysaccharidosis (44 Hurler phenotype, 17 attenuated cases) who underwent nocturnal oximetry between 6 months pre- to 16 years post-treatment (median follow-up 22 months).	A total of 150 sleep oximetry studies were analysed. SDB was defined as ODI 4% > 5 episodes/h and median SpO$_2$ <95%. Moderate SDB was diagnosed if ODI4% was 5–10 episodes/h and severe SDB as ODI4% >10 episodes/h. The incidence of SDB was 68% and 16% of participants required

				therapeutic intervention for airway obstruction. Greater frequency of SDB progression and requirement for treatment intervention were demonstrated amongst patients under enzyme replacement therapy as compared to those who underwent haematopoietic stem cell transplantation.
Coverstone et al, 2014 [94]	Retrospective, cohort study	IV	119 consecutive children with trisomy 21 (median age 6 years; range 3 months-21 years) who underwent polysomnography for suspected obstructive SDB.	A McGill oximetry score of 1-4 was calculated from the oximetry recording of polysomnography by scorers blinded to the polysomnography result and each child's clinical course. Median AHI was 4.6 episodes/h (range 0-101.8 episodes/h), median obstructive AHI was 2.5 episodes/h (range 0-101.1 episodes/h) and median central apnoea index was 1.1 episodes/h (0-35.2 episodes/h). 50% of

				patients had obstructive AHI ≥2.5 episodes/h. 49.6% of children had a McGill Score of 1 (inconclusive); their median obstructive AHI was 1.0 episode/h (interquartile range 0.4-3.3 episodes/h). McGill score was 2 in 36.1% of patients; their median obstructive AHI was 4.5 episodes/h (interquartile range 1.3-8.8 episodes/h). In 14.3% of patients the McGill score was 3 or 4; the median AHI was 16.1 episodes/h (interquartile range 9.3-45.5 episodes/h). In 10% of patients had central apnoea index was ≥2.5 episodes/h although obstructive AHI was <2.5 episodes/h) and 41.2% of them had McGill score of 2.
Robison et al, 2013 [99]	Retrospective, cohort	III	295 infants diagnosed	OSAS was graded as mild

	study		with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 months and with follow-up ≥6 months later.	(AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common interventions with average age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76 patients (20.9%, 12.8 months); supplemental oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16 patients (4.4%, 25.7 months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24

				months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following intervention was highest after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP.
Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score was 4. The presence of obstructive events and increased work of breathing was used to re-classify UAO severity if necessary. When UAO was mild, the child had a trial of prone positioning, feeding and management

				of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. The average duration of hospitalisation after nasopharyngeal airway insertion was 10 days (range 6–28 days). For infants discharged with an artificial airway, the immediate post-insertion sleep study revealed no UAO in 7.9% of cases, mild UAO in

				61.9% and moderate UAO in 30.2%. The average duration of nasopharyngeal airway use was 8 months (3 weeks to 27 months); 88.9% of infants had the nasopharyngeal airway removed before the age of 12 months. Of patients who required tracheostomy, 64.2% were decannulated at a median age of 3 years (range 2-5 years), whereas the remaining subjects continued to have tracheostomy or underwent mandibular distraction osteogenesis surgery. 82/104 (78.8%) infants required feeding with a nasogastric tube for a few weeks to months. No fatalities related to UAO were reported.
Schaefer et al, 2004 [50]	Retrospective, cohort study	IV	21 patients with isolated Pierre Robin sequence	Patients were followed for a median period of 33

			treated by one surgeon over a 9-year period; 18 of 21 infants presented during the first week of life; 3 other infants were 12-33 months old.	months (range 9-70 months). Airway patency was achieved with prone positioning for 10 (47.6%) patients, with tongue-lip adhesion for 7 of 10(47.6%) patients who underwent the procedure, with tracheostomy for 2 (9.5%) patients, and with mandibular distraction osteogenesis for 3 (14.3%) patients. There was significant change in the maxillary-mandibular discrepancy during the first 1 year of life (P <0.0001). Oromotor studies performed ≥ 3 months after reversal of tongue-lip adhesion reversal (n = 9) demonstrated no deficits in tongue function, relative to other children with cleft lip/palate. Patients should be evaluated for episodes of oxyhaemoglobin desaturation occurring

				spontaneously, during feeding, or during sleep. Patients with desaturation should be evaluated with nasopharyngosocopy and bronchoscopy.
Brouillette et al, 2000 [95]	Cross-sectional study	III	349 children (6 m.o.-18 y.o.) who were referred for polysomnography due to suspected OSAS.	Children underwent polysomnography including nocturnal oximetry with a mean sleep time of 8.1 ± 1.4 hours. OSAS was defined as a mixed/obstructive apnoea/hypopnoea index $\geq$ 1 episode/h. Oximetry was considered positive for OSAS if there were 3 or more clusters of desaturations (≥ 5 desaturations $\geq 4\%$ within 10-30 min) and ≥ 3 desaturations to <90%. Of the 93 oximetry recordings read as positive, polysomnography confirmed OSAS in 90 patients (97% positive predictive value).

				However, children with a negative or inconclusive oximetry had 47% probability of having OSAS.

3.3. In the context of which symptoms and exam findings objective tests are used to exclude the presence of OSAS?

a+b. *Snoring, apnoea, restless sleep, mouth breathing, cyanotic spells, history of apparent life-threatening events, delayed growth*

Author, year	Type of Study	Class	Subjects	Methods and findings
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. The average age at follow-up was 7.7 ± 7 months.	Indications for requesting polysomnography were: snoring (53%), nocturnal desaturations (24%), an abnormal pneumogram (5%), suspected apparent life-threatening event (5%), screening for sleep disordered breathing (4%), hypoventilation (3%), diaphragmatic flutter (2%), failed car seat testing (2%), suspected apnoea of prematurity (1%), and as a routine test before growth hormone treatment

				(1%). 40 (41%) had mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h).
Bonuck et al, 2009 [28]	Systematic review and meta-analysis	-	20 cohort studies describing changes in weight, height, IGF-1 and/or IGFBP-3 serum-levels as z-scores, percentiles or raw data following adenotonsillectomy were reviewed. Studies ranged in numbers of participants from 14 to 204 children and ages of 5 months to 15.8 years with follow-up of 1 month to 3 years.	6 of 20 studies reported growth failure in a proportion of their participants. Results of meta-analysis regarding postoperative changes compared to preoperative values were reported. Standardised height (10 studies; n=363): pooled standardised mean differences (SMD) = 0.34 (95% CI 0.20-0.47); standardised weight (11 studies; n=390): pooled SMD = 0.57 (95% CI 0.44-0.70); IGF-1 (7 studies; n=177): pooled SMD = 0.53 (95% CI 0.33-0.73); IGFBP-3: (7 studies; n=177): pooled SMD =

				0.59 (95% CI 0.34 to 0.83).
Guilleminault et al, 2000 [20]	Retrospective, cohort study	III	346 infants with history of apparent life-threatening event evaluated over a 10-year period and 46 age-matched healthy infants as controls.	Participants had recording of symptoms and signs related to SDB, sleep/wake evaluation, systematic evaluation of the face and naso-oro-pharynx, nocturnal polygraphy and follow-up evaluation. 42.6% of the patients had normal nocturnal polygraphic recording and were not different from controls at the initial evaluation and during follow-up. Obstructive breathing during sleep was demonstrated in 57.4% of patients and two-thirds of these infants had SDB symptoms and mild facial dysmorphia which was apparent at 6 months of age.
Leiberman et al, 1988 [16]	Retrospective, cohort study	IV	14 infants younger than 18 months diagnosed with OSAS by	Snoring, apnoea, failure to thrive, developmental delay and recurrent respiratory

| | | | | polysomnography or nocturnal monitoring | infections were the most common presenting symptoms. Adenotonsillectomy was accompanied by clinical improvement in 13 patients. In one case prolonged nasopharyngeal intubation was necessary. |

c. *Nasal obstruction (adenoidal hypertrophy with or without tonsillar hypertrophy, choanal atresia, pyriform aperture stenosis)*

Author, year	Type of Study	Class	Subjects	Methods and findings
Brigance et al, 2009 [100]	Retrospective, cohort study	IV	73 children with OSAS younger than 24 months	Surgical interventions included adenotonsillectomy, adenoidectomy, and tonsillectomy. Surgical treatment group improved postoperatively: mean AHI change was -9.6 episodes/h (95% CI, 5.8-13.4). The medical treatment group did not improve posttreatment: mean AHI change was -3.0 episodes/h (95% CI, -15.1 to 9.1). The difference in AHI change between surgical and medical groups was 12.56

				episodes/h (95% CI, 2.7-22.4; P = 0.01).
Samadi et al, 2003 [30]	Retrospective, cohort study	IV	78 children (newborn-18 years) with choanal atresia who were managed in an academic pediatric hospital.	Patients had an average follow-up of 35 months. Thirty-five children (45%) had unilateral atresia, and 43 children (55%) had bilateral atresia. Concomitant disorders were noted: otitis media with effusion (32%), upper and lower airway diseases (32% and 23%), cardiac anomalies (19%), and gastrointestinal tract disorders (18%). Presence of bilateral choanal atresia was significantly associated with cardiac disorders (P =0.04), CHARGE syndrome (P=0.002), OSAS (P=0.003), haematological problems (P =0.001), and prematurity or failure to thrive (P =0.006). Airway patency was established surgically in all cases.

				Average age at the first surgical procedure was 25.2 months for unilateral atresia and 2.4 months for bilateral atresia.

d. *Laryngomalacia*

Author, year	Type of Study	Class	Subjects	Methods and findings
Czechowicz et al, 2015 [79]	Retrospective, cohort study	IV	76 children with laryngomalacia who underwent supraglottoplasty at age <2 years	Somatic growth changes from the time of surgery to an average of 9 months postoperatively were recorded. BMI increased from a mean of 15.4 kg/m^2 to 18.0 kg/m^2 and BMI percentile from a mean of 34th preoperatively to 51st postoperatively. The largest BMI percentile increases were recorded in infants that were 3 months old or younger at the time of supraglottoplasty, and in those under 12 months of age, who were in the lowest BMI quintile.
Powitzky et al, 2011 [32]	Retrospective, cohort study	III	20 infants (<1 y. o.) who underwent	Patients underwent polysomnography pre- and

			supraglottoplasty for severe laryngomalacia (failure to thrive or signs of severe respiratory distress, such as cyanotic spells, severe intercostal retractions, or prolonged apnoeas with significant desaturations while awake) or moderate laryngomalacia (stridor and associated retractions or dysphagia).	post-supraglottoplasty. Outcome measures included changes in stridor, sleep-disordered breathing, swallowing, and polysomnography parameters before and after surgery. Statistically significant improvements were demonstrated postoperatively in median AHI (-6.4 episodes/h; P=0.02).
O' Connor et al , 2009 [34]	Retrospective, cohort study	IV	10 children with moderate-to-severe laryngomalacia who underwent supragtottoplasty with mean age at first presentation of 2 months and 19 days (range 30–134 days)	Polysomnography was performed before and after surgery. The mean time from preoperative polysomnography to supraglottoplasty was 12.1 days and from supraglottoplasty to post-operative polysomnography 83.2 days. The observed anatomical abnormalities were: short aryepiglottic folds (10/10 patients); prolapsing arytenoid

				mucosa (9/10); and prolapsing or omega-shaped epiglottis (4/10). Total sleep time increased from a mean of 382 min to 475 min (P=0.049) and SpO_2 from a mean of 74.8% to 87.6% (P=0.006); obstructive AHI decreased from a mean of 42.7 episodes/h to 4.47 episodes/h (P=0.009) and respiratory disturbance index from 49.9 episodes/h to 8.36 episodes/h (P=0.002), following supraglottoplasty. A non-significant improvement in mean transcutaneous carbon dioxide ($TcCO_2$) partial pressure occurred (57.1 mmHg to 52.8 mmHg) (P=0.259).
Zafereo et al, 2008 [35]	Retrospective, case cohort	IV	Ten infants with laryngomalacia and OSAS who underwent supraglottoplasty.	All 10 patients were extubated after the procedure and there were no peri- or postoperative complications.

					Postoperative nocturnal polysomnography was performed at 11 weeks postoperatively (range 2-29 weeks). Caregivers reported mild improvement (10%), significant improvement (70%), and complete resolution (20%) of stridor and snoring at 4 weeks after discharge. Marked improvements and statistically significant improvements were recorded in obstructive apnoea index, obstructive AHI, respiratory disturbance index and oxygen saturation of haemoglobin nadir (P <0.05).
Valera et al, 2006 [36]	Case series		IV	7 children with mean age 6.8 months (range 1-15 months) with severe laryngomalacia based on symptoms and flexible endoscopy	Four of the 7 children had a history of stridor, and in 3 patients without stridor the predominant symptom of upper airway obstruction was snoring. There was

				history of cyanosis on effort and increased nocturnal work of breathing or apnoea. Baseline polysomnography was performed and subsequently patients underwent epiglottoplasty with bilateral incision of the aryepiglottic folds, followed by bilateral excision of excess mucosa in the lateral arytenoid region. If epiglottis had a posterior position, epiglottopexy was carried out. Polysomnography was repeated postoperatively. Preoperatively, one of 7 patients had moderate OSAS and the remaining children had severe OSAS and all of them had paradoxical breathing; respiratory disturbance index was 5.4 to 22.8 episodes/h (mean ± SD: 11.66 ± 7.51 episodes/h); minimum SpO_2 was 70% to 94% (mean ± SD:

				81.71% ± 8.47%). Two of 7 patients with pharyngolaryngomalacia did not tolerate extubation and required tracheostomy. Of the remaining patients, 4 had marked improvement of respiratory symptoms and 1 only partial improvement of apnoea and stridor; 2 patients with feeding difficulties did not require a nasogastric tube postoperatively. At an average of 82 days after surgery, respiratory disturbance index decreased from a mean of 10 episodes/h preoperatively to a mean of 2.2 episodes/h (P <0.05); minimum SpO_2 tended to increase from 83.2% preoperatively to 86.4% postoperatively (P=0.07). Resolution of OSAS (respiratory disturbance index <1 episode/h) was not achieved in 3 patients with additional

				abnormalities: tracheomalacia; marked neurologic deficit; hypertrophy of the pharyngeal and palatine tonsils.
e. *Craniosynostosis with ro without midface hypoplasia, marked mandibular hypoplasia, cleft lip and/or palate*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Robin sequence (1 y.o.)	10 (25.6%) infants had mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients or 74.4%) had severe OSAS (AHI >10 episodes/h). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge. 30.0% of infants with mild/moderate OSAS were placed on continuous positive airway pressure during admission and 20.0% of infants at discharge. Amongst those with severe OSAS, 82.8%

				required airway interventions: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge. Infants with severe OSAS required tube feeding at discharge more frequently than infants with mild/moderate OSAS (89.7% vs 50.0%). Children were at lower weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis

				(subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was repeated within 3–6 months. OSAS was defined as obstructive AHI ≥ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI $\geq$25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease.

				The majority of patients underwent cranial vault remodeling before the age of 1 year. Treatment for OSAS was offered at a median age of 4.5 years (range 4 months-18 years old). Adenotonsillectomy was the most frequent intervention (n=20) followed by transverse widening of the hypoplastic maxilla with a hyrax expander (n=1), midface advancement (n=6), tracheostomy (n=3) or ventilation (n=2). A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.

| Abel et al, 2012 [47] | Retrospective, cohort study | IV | 104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had an oximetry study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation. | Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score was 4. The presence of obstructive events and increased work of breathing was used to re-classify UAO severity if necessary. When UAO was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated with insertion of nasopharyngeal airway |

				with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. For infants discharged with an artificial airway, the immediate post-insertion sleep study revealed no UAO in 7.9% of cases, mild UAO in 61.9% and moderate UAO in 30.2%. The average duration of nasopharyngeal airway use was 8 months (3 weeks to 27 months); 88.9% of infants had the nasopharyngeal airway removed before the age of 12 months. No fatalities related to UAO were reported.
MacLean et al, 2012 [43]	Cross-sectional study		IV	50 infants with cleft lip and/or palate prior to surgery aged 2.7 ± 2.3 months; 56% were male, and 30% had a clinical diagnosis of Pierre Robin sequence or a syndrome.	Demographics, clinical history, sleep symptoms, facial measurement and polysomnography data were recorded. 75% of infants snored frequently or constantly. The frequency

				of parent-reported difficulty with breathing during sleep was 10% for infants with isolated cleft lip and/or palate, 33% for those with syndrome, and 43% for infants with Pierre Robin sequence (P <0.05). All infants had an obstructive-mixed apnoea-hypopnoea index (OMAHI) >1 episodes/h, and 75% had an OMAHI >3 episodes/h. Infants with Pierre Robin sequence had higher OMAHI (34.3 ± 5.1 episodes/h) than infants with isolated cleft lip and/or palate (7.6 ± 1.2 episodes/h) or infants with syndromes (15.6 ± episodes/h; P <0.001). Multivariate analysis demonstrated that Pierre Robin sequence was associated with higher OMAHI (P=0.022).
Cheng et al, 2011 [49]	Case series	IV	6 infants who failed	The follow-up interval was

			treatment with CPAP out of 20 infants with Pierre Robin sequence and respiratory distress.	9 months to 6 years. All infants underwent laryngoscopy and bronchoscopy under general anesthesia which revealed glossoptosis resulting in near-complete upper airway obstruction while in the prone position. Additional obstructive lesions were found: unilateral choanal atresia, hypoplastic epiglottis, laryngomalacia, tracheal stenosis. Preoperative polysomnography demonstrated an average respiratory disturbance index >27 episodes/h. Maximum CO_2 was 56-85 mmHg. Mandibulotomy, insertion of resorbable distractors and glossopexy were performed between 26 days and 11 months of age. Serial polysomnography studies were carried out postoperatively. Average respiratory disturbance

				index decreased to 7.3 episodes/h and maximum CO_2 to 34-45 mmHg. Weight percentile increased.

f. *Neuromuscular disorders (cerebral palsy, mitochondrial disorders, spinal muscular atrophy)*

Author, year	Type of Study	Class	Subjects	Methods and findings
Mosquera et al, 2014 [53]	Retrospective, cohort study	IV	18 children with mitochondrial disorder aged 1.5-18 years (5 of 18 ≤2 y.o.); mostly non-obese	All children underwent polysomnography; SDB defined as: presence of OSAS (obstructive AHI > 1 episode/h); central sleep apnoea; hypoxaemia (SpO_2 <90% for >2% of total sleep time); or hypoventilation. SDB was present in 56% of subjects. The most common type of SDB was OSAS (diagnosed in 6/18 subjects with a mean AHI of 2.7 episodes/h).
Verrillo et al, 2014 [54]	Retrospective, cohort study	III	12 infants with spinal muscular atrophy-type 1 (mean age 5.9 months), 10 controls (mean age 4.8 months)	Patients and control infants underwent polysomnography. Infants with spinal muscular atrophy had increased sleep

				latency higher AHI compared to controls (4.77 ± 3.59 episodes/h vs 0.68 ± 0.46 episodes/h).
Testa et al, 2005 [55]	Cross-sectional study	IV	14 infants with spinal muscular atrophy 1 or 2, aged 11.7 ± 11.4 months and 28 controls aged 10.1± 8.9 months	Patients with spinal muscular atrophy had significantly higher AHI compared to controls (median 1.9 [0.4–4.6] episodes/h vs 0.3 [0–2.3] episodes/h). Thoracoabdominal asynchrony was present during the inspiratory and expiratory phases in both quiet and active sleep: phase angle in quiet sleep, phase angle in active sleep, phase relation during inspiration for a breath during active sleep and quiet sleep, phase relation during expiration for a breath during active sleep and quiet sleep were all significantly greater than that demonstrated in control participants.

Kotagal et al, 1994 [56]	Retrospective, cohort study	III	9 children with severe cerebral palsy (spastic quadriparesis, severe psychomotor retardation, seizures) aged 7 months-10.4 years, who had nosiy breathing and disturbed night sleep; 9 control subjects with history of recurrent apnoea and/or enuresis aged 11 months-10.5 years.	All children underwent polysomnography. Obstructive hypopneas were defined as respiratory events with a decrease in oral-nasal airflow signal amplitude $\geq 50\%$ and SpO_2 drop $\geq 3\%$. Respiratory disturbance index was defined as the number of apnoeas and hypopneas per hour of sleep. The mean respiratory disturbance index was 5.39 episodes/h (0.81-10.07 episodes/h) in children with cerebral palsy and 2.16 episodes/h (0-5.4 episodes/h) in controls (P<0.01). 4 children with cerebral palsy had OSAS related to adenotonsillar hypertrophy and underwent adenoidectomy or adenotonsillectomy and 1 had OSAS related to micrognathia and tracheal stenosis and was treated with tracheostomy.

g. Complex disorders (achondroplasia, Beckwith-Wiedemann syndrome, Chiari malformation, Down syndrome, mucopolysaccharidoses, Prader-Willi syndrome)

Author, year	Type of Study	Class	Subjects	Methods and findings
Achondroplasia				
White et al, 2016 [101]	Retrospective, cohort study	IV	17 children with achondroplasia who underwent MRI of the cervical spine and polysomnography at the age of 2.4 ± 3.6 years; 9 patients were younger than 1 year	All patients had an abnormal AHI (> 1.5 episodes/h) and central sleep apnoea (> 5 episodes/h) was demonstrated in 6 of 17 subjects. Five patients (29%) required foramen magnum decompression. There was no significant correlation between central sleep apnoea and abnormal MRI findings indicative of foramen magnum stenosis. Children who were operated did not differ in AHI, central apnoea index, obstructive apnoea index or desaturation index from those who were not operated. Cord compression (either associated T2 cord signal abnormality or clinical

				findings of clonus) was most predictive of subsequent surgical decompression.
Afsharpaiman et al, 2011 [102]	Retrospective, cohort study	IV	46 children aged 3 months to 14 years over a 15-year period; 25 of 46 subjects had age ≤2 years.	25 (54.3%) patients had OSAS. Mean AHI was 11.2 ± 7.3 episodes/h and minimum SpO_2 was $85.8 \pm 5.4\%$ in children ≤2 years old. Children with OSAS tended to be younger than those without OSAS. Participants aged ≤2 years had more frequently OSAS (16 of 25 or 64.0%; P=0.01) than older patients, that was significantly more severe (p=0.004) and with deeper oxyhaemoglobin desaturations (p=0.004). Amongst patients ≤2 years old, adenotonsillectomy was the only treatment intervention for 33.0% of children >2 years old compared to 24.0% of those ≤2 years old. CPAP was applied in 9.8% of

				patients >2 years old vs. 28% of those ≤2 years old. Amongst patients ≤2 years old, two children were treated with CPAP for severe OSAS that persisted or deteriorated after adenotonsillectomy and five children had only CPAP. Treatment interventions were accompanied by improvement in polysomnography indices.
Ednick et al, 2009 [57]	Retrospective, cohort study	III	12 infants with achondroplasia and 12 aged-matched control infants	Polysomnographic records for both patients and controls were reviewed. Brain MRIs in infants with achondroplasia were also reviewed to evaluate the size of the foramen magnum and assess its relationship to SDB. Infants with achondroplasia had a significant increase in total respiratory disturbance index (13.9 ±10.8 episodes/h in the

				achondroplasia group versus 2.0 ± 0.9 episodes/h in the control group; $P <0.05$). However, there was no significant difference in percentages of active sleep, quiet sleep, or sleep efficiency. Infants with achondroplasia had decreased spontaneous arousal index (10.5 ± 3.5 episodes/h in the achondroplasia group versus 18.6 ± 2.7 episodes/h in controls; $P <0.0001$) and respiratory arousals (10.3 ± 6.3 in infants with achondroplasia group versus 27.5 ± 9.5 in the control group; $P < .0001$). There were no significant correlations between the anteroposterior or transverse diameters and the respiratory disturbance index.
Beckwith-Wiedemann syndrome				
Kamata et al, 2005 [58]	Case report	-	2 infants with Beckwith-	CASE 1: Obstructive apnea

			Wiedemann syndrome who developed OSAS after 1-stage repair for omphalocele.	index was17.3 episodes/h, and SpO_2 was lower than 95% for 80% of the total sleep time. CT and MRI revealed obstruction of the upper airway between the large tongue and the hypopharynx. Central tongue resection and division of the frenulum linguae for associated ankyloglossia were performed 97 days after birth. One month postoperatively, apneic events resolved and SpO_2 was below 95% for only 1% of the total sleep time. CASE 2: Obstructive apnoea index was 28.1 episodes/h. Division of the frenulum linguae and anterior glossopexy were carried out 55 days after birth. Postoperative polysomnogram indicated a marked reduction in the obstructive apnoea index.

Chiari malformation				
Khatwa et al, 2013 [59]	Retrospective, cohort study	IV	22 children with Chiari malformation type I (11 males median age 10 years, range 1-18 years)	3 children had central sleep apnoea, 5 had OSAS and one child had both obstructive and central sleep apnoeas. Children with SDB had excessive crowding of the brainstem structures at the foramen magnum and greater length of herniation relative to children without SDB. Patients with central sleep apnoeas underwent surgical decompression, with improvement in polysomnography.
Down syndrome				
Goffinski et al, 2015 [61]	Retrospective, cohort study	IV	177 infants with Down syndrome (mean age 44 ± 48 days)	59 patients underwent polysomnography due to clinical concerns. 95% of infants had OSAS (AHI ≥2 episodes/h) and 71% of them had severe disease (AHI ≥10 episodes/h). The minimum overall prevalence of OSAS among the larger group of

				infants was 31% (56/177). Increased frequency of OSAS was identified in children with Down syndrome and dysphagia, congenital heart disease, history of premature birth, or gastroesophageal reflux disease. (mean $EtCO_2$ 58.5 $\pm$ 10.1; range 44–98 mmHg).
Jacobs et al, 1996 [103]	Retrospective, cohort study	IV	71 pediatric patients with Down syndrome and upper airway obstruction over a 5-year period	34 children had pulmonary arterial hypertension; 44 of 71 patients had multiple sites of airway obstruction. Abnormalities causing airway obstruction included lymphoid hyperplasia, macroglossia, narrow nasopharynx, laryngomalacia, congenital subglottic stenosis, tracheobronchomalacia, and tracheal stenosis. Children with upper airway obstruction underwent surgical procedures including tonsillectomy,

				adenoidectomy, tonsillar pillar plication, uvulopalatopharyngoplasty, anterior tongue reduction, tongue-hyoid suspension, laryngotracheoplasty, and tracheotomy. 27 patients had mild obstructive symptoms, and most of them improved after tonsil or adenoid surgery, or both. The remaining patients were of younger age and had more severe symptoms, multiple sites of obstruction, and high incidence of cardiac disease. 11 (39%) of the 28 patients in this group had significant residual symptoms after surgery. Four children are tracheotomy-dependent. 5 deaths occurred and 3 of them were attributed to upper airway obstruction.
Mucopolysaccharidoses				
Pal et al, 2015 [65]	Retrospective, cohort	IV	61 children with type I	A total of 150 sleep

	study			mucopolysaccharidosis (44 Hurler phenotype, 17 attenuated cases) who underwent nocturnal oximetry between 6 months pre- to 16 years post-treatment (median follow-up 22 months).	oximetry studies were analysed. SDB was defined as ODI4% > 5 episodes/h and median SpO_2 <95%. Moderate SDB was diagnosed if ODI4% was 5–10 episodes/h and severe SDB as ODI4% >10 episodes/h. The incidence of SDB was 68% and 16% of participants required therapeutic intervention for airway obstruction. Greater frequency of SDB progression and requirement for treatment intervention were demonstrated amongst patients under enzyme replacement therapy as compared to those who underwent haematopoietic stem cell transplantation.
Prader-Willi syndrome				
Cohen et al, 2014 [67]	Retrospective, cohort study	IV	44 patients with Prader-Willi (0.3-15.6 years old; 23 subjects <2 years of age)	Children aged <2 years had more frequently central sleep apnoea compared to older children (43% vs.

				5%; P = 0.003). Obstructive events were more prevalent in older children. Supplemental oxygen was used in 9 infants with Prader-Willi syndrome and central sleep apnoea and the median central apnoea index decreased from 14 to 1 episode/h (P = 0.008).
Sedky et al, 2014 [68]	Quantitative review	-	14 studies of children with Prader-Willi syndrome and who underwent polysomnography in order to exclude OSAS (n = 224 children)	Prevalence of OSAS across studies was 79.91% (179/224); 53.07% had mild OSAS, 22.35% moderate OSAS, and 24.58% severe OSAS. The prevalence of OSAS was 88.89% (32/36) in patients aged ≤2 years, 88.89% (32/36) in the > 2 to ≤ 7-year age group, 86.49% (32/37) in the > 7 to ≤ 14-year age group, and 76.19% (16/21) in the > 14 to ≤ 18-year age group (P >0.05). Younger children and those with higher BMI

				z scores had higher AHI. Narcolepsy was present in 35.71% of cases. Adenotonsillectomy was associated with improvement in OSAS for most children but residual OSAS was present in the majority of cases postoperatively.
Urquhart et al, 2013 [104]	Retrospective, cohort study	IV	10 infants (8 female) with Prader-Willi syndrome aged 0.06-1.79 (median 0.68) years.	All patients underwent full polysomnography, and supplemental oxygen was administered to those with frequent desaturations accompanying central events during sleep. They were followed with regular split-night studies (periods in room air and with supplemental oxygen). Thirty split-night studies were completed. In room air, children with Prader-Willi syndrome had a median (IQR) central apnoea index of 4.7 (1.9, 10.6) episodes/h, with

				accompanying falls in oxygen saturation (SpO_2). Oxygen supplementation was related to significant reductions in central apnoea index to 2.5 episodes/h (P=0.002), and improved SpO_2. No change in the number of obstructive events was noted. Central events were more frequent in REM/active sleep.

Topic 4: Treatment of OSAS in young children

Online Supplementary Table S4

4.1. When is OSAS in young children treated?				
a. *Apparent upper airway obstruction without or with increased work of breathing in association with OSAS*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Cote et al, 2015 [98]	Retrospective, cohort study	IV	Review of 9038 tonsillectomies performed over 7 years; 215 (2.4%) were carried out on children ≤2 years old; 74 of 215	Diagnosis of SDB was based on clinical evaluation; OSAS was diagnosed with an obstructive AHI >1.5 episodes/h; children

			underwent tonsillectomy for OSAS and 123 of 215 for SDB. Median age was 21 months (10–24 months); 2.5% of patients were <12 months old and 78.7% were >18 months old.	underwent urgent tonsillectomy without polysomnography after hospital admission for obstructive breathing patterns, oxygen desaturations and enlarged tonsils. Severe OSAS was defined as an obstructive AHI >10 episodes/h. 4.7% of tonsillectomies were performed due to previous hospitalisation for upper airway obstruction with hypertrophic tonsisls. Study data were compared with available Colorado data for each variable. The proportions of male, African-American, Hispanic, obese, underweight, premature, syndromic and daycare subjects in the cohort were significantly different than in the Colorado population. In multivariable analysis, African-Americans were at 12.5 times greater risk

				for having severe OSAS than Caucasians. Children with syndromes or craniofacial anomalies had 11 times greater risk (P < 0.0001), and patients in daycare had 2.2 times lower probability (P=0.04) of undergoing polysomnography before tonsillectomy. Weight did not influence requests for polysomnography.
Robison et al, 2013 [99]	Retrospective, cohort study	III	295 infants diagnosed with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 months and with follow-up ≥6 months later.	OSAS was graded as mild (AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common interventions with average age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76 patients (20.9%, 12.8

				months); supplemental oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16 patients (4.4%, 25.7 months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24 months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following intervention was highest after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP.
Abel et al, 2012 [47]	Retrospective, cohort	IV	104 patients with Pierre	Upper airway obstruction

	study		Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	(UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score was 4. The presence of obstructive events and increased work of breathing was used to re-classify UAO severity if necessary. When UAO was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated with insertion of

				nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. For infants discharged with an artificial airway, the immediate post-insertion sleep study revealed no UAO in 7.9% of cases, mild UAO in 61.9% and moderate UAO in 30.2%.
Powitzky et al, 2011 [32]	Retrospective, cohort study	III	20 infants (<1 y. o.) who underwent supraglottoplasty for severe laryngomalacia (failure to thrive or signs of severe respiratory distress, such as cyanotic spells, severe intercostal retractions, or prolonged apnoeas with significant desaturations while awake) or moderate laryngomalacia (stridor and associated retractions or dysphagia).	Patients underwent polysomnography pre- and post-supraglottoplasty. Outcome measures included changes in stridor, sleep-disordered breathing, swallowing, and polysomnography parameters before and after surgery. Statistically significant improvements were demonstrated postoperatively in median AHI (-6.4 episodes/h; P=0.02).

Sher et al, 1986 [52]	Retrospective, cohort study	IV	33 patients with craniofacial abnormalities and upper airway obstruction with ages 0 to 24 years.	Patients underwent polysomnography, nasopharyngoscopy and cephalometry. Obstruction at the oropharyngeal level was classified in 4 categories: i) posterior movement of the tongue towards the posterior pharyngeal wall; ii) compression of the soft palate on the posterior pharyngeal wall by the tongue; iii) collapse of the lateral pharyngeal walls; iv) circular constriction of the pharynx. Nasopharyngeal tube, glossopexy, mandibular advancement or tracheostomy were selected based on endoscopic findings.
b. *Abnormalities in polysomnography, polygraphy or pulse oximetry parameters in combination with ALTE, snoring, nocturnal tachypnea, oral breathing or delayed growth*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Czechowicz et al, 2015	Retrospective, cohort	IV	76 children with	Somatic growth changes

| [79] | study | | laryngomalacia who underwent supraglottoplasty at age <2 years | from the time of surgery to an average of 9 months postoperatively were recorded. BMI increased from a mean of 15.4 kg/m^2 to 18.0 kg/m^2 and BMI percentile from a mean of 34th preoperatively to 51st postoperatively. The largest BMI percentile increases were recorded in infants that were 3 months old or younger at the time of supraglottoplasty, and in those under 12 months of age, who were in the lowest BMI quintile. |
| Nachalon et al, 2014 [78] | Prospective, cohort study | IV | 20 children (6-36 m.o.) diagnosed with OSAS (obstructive AHI >5 episodes/h) | Children were evaluated before and 5 ± 2 months after adenotonsillectomy and height, weight, circulating high sensitive C-reactive protein (CRP), and insulin-like growth factor 1 (IGF-1) levels were measured. Caloric intake was assessed by a validated Short Food |

				Frequency Questionnaire (SFFQ). Postoperatively, children had mean increase of 4.81 cm in height and 1.88 kg in weight (P < 0.001 for both) and a significant increase in BMI Z score (P = 0.002). Increased caloric intake (mean 377 kcal/day) was recorded (P < 0.001), with increased protein and decreased fat intake. Reduction in CRP levels correlated with the increase in body weight in boys (P < 0.05 after adjustment for caloric intake).
Leonardis et al., 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to

				treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40 patients had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS.68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia

				(28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: antireflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy (7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration and blood transfusion for prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari

				decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale). Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%).

Greenfeld et al, 2003 [15]	Prospective, cohort study	IV	29 consecutive infants <18 months of age who underwent polysomnography (PSG) and were diagnosed with OSAS due to adenotonsillar hypertrophy	A paediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of OSAS symptoms post-treatment was collected. Two infants underwent adenoidectomy only and the rest of them had adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants. Other symptoms included: sleep apnoea (72%), frequent movements during sleep (69%), mouth breathing (62%) and recurrent awakenings (38%). Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$

				percentile to the $42^{nd} \pm 32^{nd}$ percentile (P<0.001). 14/29 (48%) of the infants dropped two or more major percentiles prior to surgery. Following surgery, significant weight gain increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P<0.0001). 5 of 29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3/5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was documented in 6 of 23 (26%) of infants and repeat adenoidectomy was required.
c. *Abnormalities in polysomnography, polygraphy or pulse oximetry parametres in association with adenotonsillar hypertrophy, choanal atresia, laryngomalacia, midface hypoplasia, mandibular hypoplasia, neuromuscular disorders*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Ramgopal et al, 2014 [25]	Retrospective, cohort	IV	97infants (59 males; mean	40 (41%) had

	study			age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. The average age at follow-up was 7.7 ± 7 months.	mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h). 47 patients (48%) were observed or received anti-reflux medications; 27 patients (25%) required non-surgical intervention (CPAP in 85% of cases and oxygen therapy in 15% of patients); 36 patients (37%) were treated primarily surgically (tonsillectomy, adenoidectomy, adenotonsillectomy, supraglottoplasty, mandibular distraction, total calvarial release of suture, and sublabial repair). 38 patients were followed up with repeat polysomnography after a median interval of 8 months (range 1-24 months) and 68% of infants had resolution of

				symptoms and improvement of polysomnography findings; 27 infants were followed clinically after a mean interval of 5 months (range 1-34.5 months) and symptoms resolved in 85% of patients. The likelihood of symptom resolution was higher with surgical management than with oxygen therapy/CPAP (OR 4.75; P<0.01), but it did not differ significantly between medical management and oxygen therapy/CPAP (P>0.05). Likelihood of symptom resolution did not differ between patients who received medications and those with surgical treatment (P >0.05). Symptom improvement was more likely in children who underwent medical or surgical treatment compared to no

				treatment (OR 4.57; P=0.01 and OR 7.24; P=0.002, respectively). There was no significant difference in symptom resolution between children who were treated with oxygen therapy/CPAP and those who were left untreated (P=0.49).
Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Robin sequence (1 y.o.)	10 (25.6%) infants had mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients or 74.4%) had severe OSAS (AHI >10 episodes/h). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge.30.0% of infants with mild/moderate OSAS were placed on continuous positive airway pressure during admission and

				20.0% of infants at discharge. Amongst those with severe OSAS, 82.8% required airway interventions: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge. Infants with severe OSAS required tube feeding at discharge more frequently than infants with mild/moderate OSAS (89.7% vs 50.0%). Children were at lower weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface

				hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was repeated within 3–6 months. OSAS was defined as obstructive AHI $\geq$ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI $\geq$25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to

				snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. The majority of patients underwent cranial vault remodeling before the age of 1 year. Treatment for OSAS was offered at a median age of 4.5 years (range 4 months-18 years old). Adenotonsillectomy was the most frequent intervention (n=20) followed by transverse widening of the hypoplastic maxilla with a hyrax expander (n=1), midface advancement (n=6), tracheostomy (n=3) or ventilation (n=2). A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without

				midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.
Leonardis et al., 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40

				patients had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS.68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%),

				adenotonsillectomy (7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration and blood transfusion in cases of prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on

				caregivers' scale). Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%).
Robison et al, 2013 [99]	Retrospective, cohort study	III	295 infants diagnosed with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 months and with follow-up ≥6 months later.	OSAS was graded as mild (AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common interventions with average age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76

				patients (20.9%, 12.8 months); supplemental oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16 patients (4.4%, 25.7 months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24 months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following intervention was highest after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP.

Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 1; moderate if the McGill oximetry score was 2; and severe if the McGill oximetry score was 3. The presence of obstructive events and increased work of breathing was used to re-classify UAO severity if necessary. When UAO was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated

				with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. For infants discharged with an artificial airway, the immediate post-insertion sleep study revealed no UAO in 7.9% of cases, mild UAO in 61.9% and moderate UAO in 30.2%. The median follow-up was 12 months (range 2–30 months). Only 7 of 63 (11.1%) patients had the airway in situ for more than 12 months.
Cheng et al, 2011 [49]	Case series	IV	6 infants who failed treatment with CPAP out of 20 infants with Pierre Robin sequence and respiratory distress.	The follow-up interval was 9 months to 6 years. All infants underwent laryngoscopy and bronchoscopy under general anesthesia which revealed glossoptosis resulting in near-complete

				upper airway obstruction while in the prone position. Additional obstructive lesions were found: unilateral choanal atresia, hypoplastic epiglottis, laryngomalacia, tracheal stenosis. Preoperative polysomnography demonstrated an average respiratory disturbance index >27 episodes/h. Maximum CO_2 was 56-85 mmHg. Mandibulotomy, insertion of resorbable distractors and glossopexy were performed between 26 days and 11 months of age. Serial polysomnography studies were carried out postoperatively. Average respiratory disturbance index decreased to 7.3 episodes/h and maximum CO_2 to 34-45 mmHg. Weight percentile increased.

Shatz et al, 2004 [105]	Retrospective, cohort study	IV	24 infants younger than 1 year with upper airway obstruction, obstructing adenoids and OSAS but no other abnormalities.	Presenting symptoms (including apnoea episodes), physical examination findings, and results of polysomnography, endoscopy, pHmetry, and echocardiography were reviewed. With careful preoperative and postoperative monitoring, all 24 infants underwent adenoidectomy without complications. All patients had marked improvement with complete resolution of upper airway obstruction symptoms, failure to thrive, and gastroesophageal reflux disease.
Greenfeld et al, 2003 [15]	Prospective, cohort study	IV	29 consecutive infants <18 months of age who underwent polysomnography (PSG) and were diagnosed with OSAS due to adenotonsillar	A pediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of OSAS symptoms post-treatment was collected.

				hypertrophy	Two infants underwent adenoidectomy only and the rest of them had adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants. Other symptoms included: sleep apnoea (72%), frequent movements during sleep (69%), mouth breathing (62%) and recurrent awakenings (38%). Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$ percentile to the $42^{nd} \pm 32^{nd}$ percentile (P<0.001). 14 of 29 (48%) of the infants dropped two or more major percentiles prior to surgery. Following surgery,

				significant weight gain increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P<0.0001). 5 of 29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3 of 5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was documented in 6 of 23 (26%) of infants and repeat adenoidectomy was required.

4.2. Are there complex conditions predisposing to upper airway obstruction which make treatment of OSAS a priority?				
a. *Achondroplasia*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Ednick et al, 2009 [57]	Retrospective, cohort study	III	12 infants with achondroplasia and 12 aged-matched control infants	Polysomnographic records for both patients and controls were reviewed. Brain MRIs in infants with

				achondroplasia were also reviewed to evaluate the size of the foramen magnum and assess its relationship to SDB. Infants with achondroplasia had a significant increase in total respiratory disturbance index (13.9 ± 10.8 episodes/h in the achondroplasia group versus 2.0 ± 0.9 episodes/h in the control group; $P <0.001$). However, there was no significant difference in percentages of active sleep, quiet sleep, or sleep efficiency. Infants with achondroplasia had decreased spontaneous arousal index (10.5 ± 3.5 episodes/h in the achondroplasia group versus 18.6 ± 2.7 episodes/h in controls; $P <0.0001$) and respiratory arousals (10.3 ± 6.3 in infants with

				achondroplasia group versus 27.5 ± 9.5 in the control group; $P <0.0001$). There were no significant correlations between the anteroposterior or transverse diameters and the respiratory disturbance index.
b. *Beckwith-Wiedemann syndrome*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Kamata et al, 2005 [58]	Case report	-	2 infants with Beckwith-Wiedemann syndrome who developed OSAS after 1-stage repair for omphalocele.	CASE 1: Obstructive apnoea index was 17.3 episodes/h, and SpO2 was lower than 95% for 80% of the total sleep time. Computed tomography and magnetic resonance imaging revealed obstruction of the upper airway between the large tongue and the hypopharynx. Central tongue resection and division of the frenulum linguae for associated ankyloglossia were performed 97 days after

				birth. One month postoperatively, apneic events resolved and SpO2 was below 95% for only 1% of the total sleep time. CASE 2: Obstructive apnoea index was28.1 episodes/h. Division of the frenulum linguae and anterior glossopexy were carried out 55 days after birth. Postoperative polysomnogram indicated a marked reduction in the obstructive apnoea index.
c. *Chiari malformation*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Khatwa et al, 2013 [59]	Retrospective, cohort study	IV	22 children with Chiari malformation type I (11 males median age 10 years, range 1-18 years)	3 children had central sleep apnoea, 5 had OSAS and one child had both obstructive and central sleep apnoeas. Children with SDB had excessive crowding of the brainstem structures at the foramen magnum and greater length of herniation relative to children

				without SDB. Patients with central sleep apnoeas underwent surgical decompression, with improvement in polysomnography.
d. *Down syndrome*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Goffinski et al, 2015 [61]	Retrospective, cohort study	IV	177 infants with Down syndrome	59 patients underwent polysomnography due to clinical concerns. 95% of infants had OSAS (AHI ≥2 episodes/h) and 71% of them had severe disease (AHI ≥10 episodes/h). The minimum overall prevalence of OSAS among the larger group of infants was 31% (56 of 177). Significant relationships were identified between OSAS and dysphagia (aspiration or significant pharyngeal penetration during feeding on video fluoroscopic swallow study), congenital heart

				disease (atrial septal defects, ventricular septal defects, atrioventricular canal defects, tetralogy of Fallot, aortic coarctation, and patent ductus arteriosus), prematurity, gastroesophageal reflux disease, and other gastrointestinal conditions(duodenal atresia, duodenal stenosis, tracheoesophageal fistula, malrotation or Hirschsprung disease). Co-occurrence of dysphagia and congenital heart disease predicted the occurrence of OSAS in 36% of cases with a positive predictive value of 71%. The risk of OSAS was significantly higher among infants with gastrointestinal conditions compared to infants without such conditions (OR 2.92; 95% CI 1.75-4.09; P=0.002).

Linz et al, 2013 [106]	Retrospective, cohort study	IV	51 infants with Down syndrome and mean age 2.7 months who underwent polysomnography.	OSAS was defined as a mixed-obstructive apnoea index ≥1 episode/h. Twenty-seven infants (53%) had OSAS. Median mixed-obstructive index decreased from 2.3 (1 to 13) episodes/h to 0 (0 to 0.2 episodes/h; $P < 0.05$) following oral appliance placement. Seven of these infants were treated with an appliance that included some type of velar extension to move the tongue base forward.
e. *Mucopolysaccharidoses*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Pal et al, 2015 [65]	Retrospective, cohort study	IV	61 children with type I mucopolysaccharidosis (44 Hurler phenotype, 17 attenuated cases) who underwent nocturnal oximetry between 6 months pre- to 16 years post-treatment (median follow-up 22 months).	A total of 150 sleep oximetry studies were analysed. SDB was defined as ODI 4% > 5 episodes/h and median SpO_2 <95%. Moderate SDB was diagnosed if ODI4% was 5–10 episodes/h and severe SDB as ODI4% >10

				episodes/h. The incidence of SDB was 68% and 16% of participants required therapeutic intervention for airway obstruction. Greater frequency of SDB progression and requirement for treatment intervention were demonstrated amongst patients under enzyme replacement therapy as compared to those who underwent haematopoietic stem cell transplantation.

f. *Prader-Willi syndrome*

Author, year	Type of Study	Class	Subjects	Methods and findings
Sedky et al, 2014 [68]	Quantitative review	-	14 studies of children with Prader-Willi syndrome and who underwent polysomnography in order to exclude OSAS (n = 224 children)	Prevalence of OSAS (AHI >5 episodes/h across studies was 79.91% (179/224); 53.07% had mild OSAS, 22.35% moderate OSAS, and 24.58% severe OSAS. The prevalence of OSAS was 88.89% (32/36) in patients aged ≤2 years, 88.89% (32/36) in the > 2 to ≤ 7-

				year age group, 86.49% (32/37) in the > 7 to ≤ 14-year age group, and 76.19% (16/21) in the > 14 to ≤ 18-year age group (P >0.05). Younger children and those with higher BMI z scores had higher AHI. Narcolepsy was present in 35.71% of cases. Adenotonsillectomy was associated with improvement in OSAS for most children but residual OSAS was present in the majority of cases postoperatively.

Online Supplementary Table S5

Topic 5: Stepwise treatment approach for OSAS in young children

5.1. What is the hierarchy of treatment interventions for OSAS in young children?				
a. *Treatment interventions for OSAS in young children are individualised according to etiology, severity and morbidity*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Cote et al, 2015 [98]	Retrospective, cohort	IV	Review of 9038	Diagnosis of SDB was

	study		tonsillectomies performed over 7 years; 215 (2.4%) were carried out on children ≤2 years old; 74 of 215 underwent tonsillectomy for OSAS and 123 of 215 for SDB. Median age was 21 months (10–24 months); 2.5% of patients were <12 months old and 78.7% were >18 months old.	based on clinical evaluation; OSAS was diagnosed with an obstructive AHI >1.5 episodes/h; children underwent urgent tonsillectomy without polysomnography after hospital admission for obstructive breathing patterns, oxygen desaturations and enlarged tonsils. Severe OSAS was defined as an obstructive AHI >10 episodes/h. 4.7% of tonsillectomies were performed due to previous hospitalisation for upper airway obstruction with hypertrophic tonsisls. Study data were compared with available Colorado data for each variable. The proportions of male, African-American, Hispanic, obese, underweight, premature, syndromic and daycare subjects in the cohort were significantly different than

				in the Colorado population. In multivariable analysis, African-Americans were at 12.5 times greater risk for having severe OSAS than Caucasians. Children with syndromes or craniofacial anomalies had 11 times greater risk (P < 0.0001), and patients in daycare had 2.2 times lower probability (P=0.04) of undergoing polysomnography before tonsillectomy. Weight did not influence requests for polysomnography.
Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Robin sequence (1 year old)	10 (25.6%) infants had mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients or 74.4%) had severe OSAS (AHI >10 episodes/h). 24 (61.5%) had other abnormalities: Stickler syndrome (n=7), chromosomal

				abnormalities (n=4), dysmorphic or syndromic features (n=7), cardiac abnormalities (n=4). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge. 30.0% of infants with mild/moderate OSAS were placed on continuous positive airway pressure during admission and 20.0% of infants at discharge. Amongst those with severe OSAS, 82.8% required airway interventions as an inpatient, 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge. Infants with severe OSAS required tube feeding at discharge more frequently than infants with

				mild/moderate OSAS (89.7% vs 50.0%). Children were at lower weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was repeated within 3–6

				months. OSAS was defined as obstructive AHI $\geq$ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI $\geq$25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. The majority of patients underwent cranial vault remodeling before the age of 1 year. Treatment for OSAS was offered at a median age of 4.5 years (range 4 months-18 years old). Adenotonsillectomy was

				the most frequent intervention (n=20) followed by transverse widening of the hypoplastic maxilla with a hyrax expander (n=1), midface advancement (n=6), tracheostomy (n=3) or ventilation (n=2). A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.
Robison et al, 2013 [99]	Retrospective, cohort study	III	295 infants diagnosed with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 montsh and with follow-up ≥6 months later.	OSAS was graded as mild (AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common interventions with average

				age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76 patients (20.9%, 12.8 months); supplemental oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16 patients (4.4%, 25.7 months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24 months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following intervention was highest

				after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP.
Li et al, 2002 [107]	Retrospective cohort study	IV	110 children with Pierre Robin sequence (64 with cleft palate); 85% of patients ≤ 3 months old	Prone posturing was effective in the treatment of mild airway obstruction in 82 patients with noisy breathing. 28 infants were intubated due to severely increased work of breathing; 7 had a tongue-to-lip adhesion and 3 of them had relief of upper airway obstruction whereas in the remaining rupture of the wound occurred and they underwent tracheostomy; 2 additional patients had tracheostomy without any other intervention; patients with tracheostomy were decannulated successfully. 1 of 2 patients who had insertion of a nasopharyngeal tube was

				relieved temporarily. 46 patients required nasogastric tube feeding; none of the patients required gastrostomy.
b. *Nasopharyngoscopy and drug induced sedation endoscopy can be used to select appropriate treatment interventions*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Boudewyns et al, 2017 [108]	Retrospective, cohort study	IV	28 children, aged 1.3–1.8 years who had upper airway surgery directed by drg-induced sleep endoscopy.	BMI-z score was −0.7 to 1.3 and obstructive AHI was 7.5–28.3 episodes/h. 25 patients had >50% obstruction at the level of the adenoids, and 23 had >50% tonsillar obstruction. Collapse of the epiglottis was demonstrated in 6 patients and late-onset laryngomalacia in 4 patients. Circumferential narrowing/collapse at the oropharyngeal or hypopharyngeal level was found in 5 children. Half of the participants had multilevel airway obstruction. Treatment interventions included

				adenoidectomy (n = 4), tonsillectomy (n = 1), and adenotonsillectomy (n = 23). One child received pre-operative CPAP treatment due to severe OSAS. Postoperatively, median obstructive AHI decreased from 13.8 episodes/h (7.5–28.3) to 0.9 episodes/h (0.4–2.4); P < 0.001.
Marques et al, 2001 [109]	Prospective, cohort study	IV	62 infants with Pierre Robin sequence aged <6 m.o.; 53.2% of infants had isolated Pierre Robin sequence	All patients underwent nasopharyngoscopy. Upper airway obstruction was classified in 4 types according to Sher et al (1992). 75.8% of infants (90.9% of those with isolated Pierre Robin sequence) had type 1 obstruction; 12.9% type 2 obstruction; 6.5% type 3 obstruction; and 4.8% type 4 obstruction. Response to treatment was defined as good pulmonary

				ventilation, reduced work of breathing and apnoea, oxygen saturation of haemoglobin >90% and tolerance of oral feeding. Prone positioning or nasopharyngeal airway insertion were adequate interventions in 76.6% and 50% of patients with type 1 or type 2 obstruction, respectively; 14.5% of infants with type 1 obstruction underwent glossopexy. The remaining infants and 100% of those with type 3 or type 4 obstruction required tracheostomy (overall frequency of tracheostomy 20.9%). Overall fatality rate was 11.3%.
Sher et al, 1992 [51]	Retrospective, cohort study	IV	53 infants with Robin sequence aged 1 day to 9 months.	All infants underwent nasopharyngoscopy and type of obstruction was classified according to Sher et al, 1986:

				Type I obstruction in 58.5% of infants; type II in 20.8%; type III in 9.4%; and type IV in 9.4% of infants. 48 (90.6%) patients responded well to insertion of nasopharyngeal tube. 24 infants (all with type I obstruction) underwent glossopexy. 7 infants with pharyngeal obstruction types II-IV who did not respond to insertion of nasopharyngeal tube required tracheostomy.
Sher et al, 1986 [52]	Retrospective, cohort study	IV	33 patients with craniofacial abnormalities and upper airway obstruction with ages 0 to 24 years.	Patients underwent polysomnography, nasopharyngoscopy and cephalometry. Obstruction at the oropharyngeal level was classified in 4 categories: i) posterior movement of the tongue towards the posterior pharyngeal wall; ii) compression of the soft palate on the posterior

				pharyngeal wall by the tongue; iii) collapse of the lateral pharyngeal walls; iv) circular constriction of the pharynx. Nasopharyngeal tube, glossopexy, mandibular advancement or tracheostomy were selected based on endoscopic findings.
c. *Overall efficacy of surgical treatment, oxygen administration, anti-reflux medications and CPAP application*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely) out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. 53% of children had genetic abnormalities including Down syndrome. The average age at follow-up was 7.7 ± 7 months.	40 (41%) had mild OSAS (1-5 episodes/h), 19 (20%) had moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h). 47 patients (48%) were observed or received anti-reflux medications; 27 patients (25%) required non-surgical intervention (CPAP in 85% of cases and oxygen therapy in 15% of patients); 36

				patients (37%) were treated primarily surgically (tonsillectomy, adenoidectomy, adenotonsillectomy, supraglottoplasty, mandibular distraction, total calvarial release of suture, and sublabial repair). 38 patients were followed up with repeat polysomnography after a median interval of 8 months (range 1-24 months) and 68% of infants had resolution of symptoms and improvement of polysomnography findings; 27 infants were followed clinically after a mean interval of 5 months (range 1-34.5 months) and symptoms resolved in 85% of them. The likelihood of symptom resolution was higher with surgical management than with oxygen therapy/CPAP (OR 4.75;

				P<0.01), but it did not differ significantly between medical management and oxygen therapy/CPAP (P>0.05). The likelihood of symptom resolution did not differ between patients who received medications and those who underwent surgical treatment (P >0.05). Symptom improvement was more likely in children who underwent medical or surgical treatment compared to no treatment (OR 4.57; P=0.01 and OR 7.24; P=0.002, respectively). There was no significant difference in symptom resolution between children who were treated with oxygen therapy/CPAP and those who were left untreated (P=0.49).

| Leonardis et al., 2013 [89] | Retrospective, cohort study | IV | 126 neonates and infants (aged 0-12 months) diagnosed with OSAS | Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40 patients had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS. 68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial |

				malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy (7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration and blood transfusion in cases of

				prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale). Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean %

				reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%).
Robison et al, 2013 [99]	Retrospective, cohort study	III	295 infants diagnosed with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 montsh and with follow-up ≥6 months later.	OSAS was graded as mild (AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common interventions with average age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76 patients (20.9%, 12.8 months); supplemental oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16

				patients (4.4%, 25.7 months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24 months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following intervention was highest after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP.

5.2. What is the efficacy of anti-reflux medications for OSAS related to gastroesophageal reflux in young children?

Author, year	Type of Study	Class	Subjects	Methods and findings
Ramgopal et al, 2014 [25]	Retrospective, cohort study	IV	97 infants (59 males; mean age 4.6 ± 3.3 months; 27.8% born prematurely)	40 (41%) had mild OSAS (1-5 episodes/h), 19 (20%) had

			out of 281 were diagnosed with OSAS (AHI ≥1 episode/h) over a 7-year period. 53% of children had genetic abnormalities including Down syndrome. The average age at follow-up was 7.7 ± 7 months.	moderate OSAS (5-10 episodes/h), and 38 (39%) had severe OSAS (>10 episodes/h); 30% of children had gastroesophageal reflux. 47 patients (48%) were observed or received anti-reflux medications; 27 patients (25%) required non-surgical intervention (CPAP in 85% of cases and oxygen therapy in 15% of patients); 36 patients (37%) were treated primarily surgically (tonsillectomy, adenoidectomy, adenotonsillectomy, supraglottoplasty, mandibular distraction, total calvarial release of suture, and sublabial repair). 38 patients were followed up with repeat polysomnography after a median interval of 8 months (range 1-24 months) and 68% of infants had resolution of

				symptoms and improvement of polysomnography findings; 27 infants were followed clinically after a mean interval of 5 months (range 1-34.5 months) and symptoms resolved in 85% of them. The likelihood of symptom resolution was higher with surgical management than with oxygen therapy/CPAP (OR 4.75; P<0.01), but it did not differ significantly between medical management and oxygen therapy/CPAP (P>0.05). The likelihood of symptom resolution did not differ between patients who received medications and those who underwent surgical treatment (P >0.05). Symptom improvement was more likely in children who underwent medical or surgical treatment compared to no treatment

				(OR 4.57; P=0.01 and OR 7.24; P=0.002, respectively). There was no significant difference in symptom resolution between children who were treated with oxygen therapy/CPAP and those who were left untreated (P=0.49).
Leonardis et al., 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or

				resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40 patients had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS. 68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy

				(23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy (7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration and blood transfusion in cases of prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of

				subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale). Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%). A mean decrease in AHI by 45.5% was demonstrated in infants treated with antireflux medications; other interventions may have had an effect.
Hartl and Chadha, 2012 [110]	Systematic review and meta-analysis		27 studies including 1295 infants with laryngomalacia	Taking under consideration that reflux definitions were variable, the estimated reflux

				prevalence in infants with laryngomalacia was 59%. Using data from 4 studies, pooled odds ratio for the presence of reflux in laryngomalacia vs. other respiratory diagnoses was 1.15 (95% CI 0.61-2.17; P = 0.67. Further evidence supporting an association between reflux and LM included the ubiquity of acid reflux using dual-probe pH monitoring in children with LM (2 studies; n = 84), the increased prevalence of reflux in severe as compared with mild LM (3 studies; n = 237; pooled OR = 9.86; P < 0.0001). Patients suffering from moderate to severe laryngomalacia were significantly more likely to have reflux than patients with mild laryngomalacia (P<0.05). There is no consistent evidence that anti-reflux treatment

				improves symptoms related to laryngomalacia including apnoeas.

5.3. What are the efficacy and risks of adenotonsillectomy in young children with OSAS?

a+b+c. *Adenotonsillectomy: efficacy, residual disease and complications*

Author, year	Type of Study	Class	Subjects	Methods and findings
Boudewyns et al, 2017 [108]	Retrospective, cohort study	IV	28 children, aged 1.3–1.8 years who had upper airway surgery directed by drug-induced sleep endoscopy.	BMI-z score was −0.7 to 1.3 and obstructive AHI was 7.5–28.3 episodes/h. 25 patients had >50% obstruction at the level of the adenoids, and 23 had >50% tonsillar obstruction. Collapse of the epiglottis was demonstrated in 6 patients and late-onset laryngomalacia in 4 patients. Circumferential narrowing/collapse at the oropharyngeal or hypoharyngeal level was found in 5 children. Half

				of the participants had multilevel airway obstruction. Treatment interventions included adenoidectomy (n = 4), tonsillectomy (n = 1) and adenotonsillectomy (n = 23). One child received pre-operative CPAP treatment due to severe OSAS. Postoperatively, median obstructive AHI decreased from 13.8 episodes/h (7.5–28.3) to 0.9 episodes/h (0.4–2.4 episodes/h; P < 0.001).
Cote et al, 2015 [98]	Retrospective, cohort study	IV	Review of 9038 tonsillectomies performed over 7 years; 215 (2.4%) were carried out on children ≤2 years old; 74 of 215 underwent tonsillectomy for OSAS and 123 of 215 for SDB. Median age was 21 months (10–24 months); 2.5% of patients	Diagnosis of SDB was based on clinical evaluation; OSAS was diagnosed with an obstructive AHI >1.5 episodes/h; children underwent urgent tonsillectomy woithout polysomnography after hospital admission for obstructive breathing

				were <12 months old and 78.7% were >18 months old.	patterns, oxygen desaturations and enlarged tonsils. Severe OSAS was defined as an obstructive AHI >10 episodes/h. Study data were compared with available Colorado data for each variable. The proportions of male, African-American, Hispanic, obese, underweight, premature, syndromic and daycare subjects in the cohort were significantly different than in the Colorado population. In multivariable analysis, African-Americans were at 12.5 times greater risk for having severe OSAS than Caucasians. Children with syndromes or craniofacial anomalies had 11 times greater risk (P < 0.0001), and patients in daycare had 2.2 times lower probability (P=0.04) of undergoing polysomnography before

				tonsillectomy. Weight did not influence requests for polysomnography.
Cheng & Elden, 2013 [111]	Retrospective, cohort study	IV	Sixty-two patients aged ≤12 months who underwent adenoidectomy (n=36) or adenotonsillectomy	Of 36 children who had adenoidectomy alone, 8 (22.2%) developed recurrent or persistent symptoms and underwent tonsillectomy at an average of 18.8 months later (range, 6–36 months). 25 patients were treated with adenotonsillectomy. Pre- and postoperative polysomnographies were available for 4 otherwise healthy patients and 3 of them had a postoperative AHI <5 episodes/h. In the medically complicated group (cerebral palsy, Crouzon syndrome, chromosomal abnormalities, cardiac anomalies, prematurity) pre-and postoperative

				polysomnography (n=7) did not demonstrate a significant change in AHI or SpO_2 nadir. Complications following adenotonsillectomy occurred in 25% of the otherwise healthy patients and in 33.3% of the complicated cases.
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was

				repeated within 3–6 months. OSAS was defined as obstructive AHI ≥ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI ≥25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. The majority of patients underwent cranial vault remodeling before the age of 1 year. Treatment for OSAS was offered at a median age of 4.5 years (range 4 months-18 years old).

				Adenotonsillectomy was the most frequent intervention (n=20) followed by transverse widening of the hypoplastic maxilla with a hyrax expander (n=1), midface advancement (n=6), tracheostomy (n=3) or ventilation (n=2). A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.
Nath et al, 2013 [112]	Retrospective, cohort study	IV	283 patients (mean age, 22 ± 7 months) who underwent adenotonsillectomy had preoperative polysomnography and 70	In the group with both preoperative and postoperative polysomnography, there were statistically significant improvements

				of them had also postoperative polysomnography.	in AHI (from 34.8 ± 40.7 episodes/h to 5.7 ± 13.8 episodes/h; P <0.001), baseline SpO_2 (from 96.6% ± 2.1% to 97.2% ± 1.4%; P = 0.05), minimum SpO_2 (from 77.2% ± 11.4% to 89.9% ± 6.8%; P <0.001), and sleep efficiency (from 84.7% ± 14.9% to 88.7% ± 9.1%; P = 0.02) after adenotonsillectomy. When AHI >5 episodes/h was used to define OSAS, 21% of the patients had residual disease. The most consistent predictor of residual OSAS postoperatively was the severity of preoperative disease (P = 0.02).
Robison et al, 2013 [99]	Retrospective, cohort study		III	295 infants diagnosed with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 months and with follow-up ≥6 months later.	OSAS was graded as mild (AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common

				interventions with average age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76 patients (20.9%, 12.8 months); supplemental oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16 patients (4.4%, 25.7 months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24 months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following

				intervention was highest after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP.
Spencer & Jones, 2012 [113]	Retrospective, cohort study	IV	86 patients with mean age 27.5 months (13-35 months) who underwent adenotonsillectomy (96.5% for obstructive airway-related disease). Patients with severe OSAS or medical comorbidities were not included in the analysis.	80 (93.0%) children did not have any intraoperative or postoperative complications. Dehydration was the most common complication and was the cause of all documented readmissions (4.7%) in patients with age from 14 to 30 months at postoperative days 2-6. One child was treated for reactive airway disease and one for postoperative fever in the post-anaesthesia care unit.
McCormick et al, 2011 [114]	Retrospective, cohort study	IV	993 patients who underwent adenoidectomy,	The most frequent pre-operative symptoms were witnessed apnoeas (n =

| | | | tonsillectomy or adenotonsillectomy with mean age 2.94 years; 499 were 1–2 years old; and 494 were 3 years old. | 736; 74.1%) and snoring (n = 588, 59.2%). The frequency of tonsil and adenoid size ≥ 3+ was 60.4% and 43.3%, respectively. The most common co-morbidities were recurrent/chronic otitis media (n = 391, 39.4%) and asthma (n = 158, 15.9%); other comorbidities were: gastroesophageal reflux, prematurity, craniofacial or airway abnormality, seizure disorder, cardiovascular anomalies, Down syndrome, failure to thrive. Pre-operative polysomnograms were available in 53 patients who had an average AHI of 18.6 episodes/h (range 2.1–60) and average SpO_2 nadir of 76.9% (range 55–90%). 700 children were hospitalized with a mean length-of-stay of 1.22 days (range 0-9 days) and a mean time-to-oral intake |

				of 0.28 days (range 0-4 days). 102 complications in 98 (9.9%) children occurred; 35 complications occurred on post-operative days 0-1 (3.5%), and 23 of them were airway-related (2.3%). Significant predictors of complications in post-operative days 0-1 were: nasal obstruction, gastroesophageal reflux disease, prematurity and a history of cardiovascular anomalies. Significant predictors of airway complications during postoperative days 0-1 were younger age (1-2 years old), larger adenoid size, nasal obstruction, and a history of cardiovascular anomalies.
Brigance et al, 2009 [100]	Retrospective, cohort study	IV	73 infants younger than 24 months who were treated for OSAS	Surgical treatment included adenotonsillectomy,

				adenoidectomy, or tonsillectomy. The surgical treatment group improved postoperatively: mean AHI change was -9.6 (95% CI, 5.8-13.4) episodes/h. The medical treatment group (observation, oxygen or CPAP) did not improve: mean AHI change was -3.0 (95% CI, -15.1 to 9.1) episodes/h. The difference in AHI change between surgical and medical groups was 12.56 (95% CI 2.7-22.4) episodes/h (P = 0.01). Eleven (18%) children had postoperative complications: postoperative respiratory distress (n=10); delayed postoperative hemorrhage (n=1); prolonged poor oral intake (n=1). Four children required intubation (2-12 days); 3 required supplemental oxygen ($\leq$2 days); 1 patient was treated with

				BPAP (1 day), and 1 with CPAP (7 days). In addition, 1 child needed replacement of a tracheotomy tube because of crusting and obstruction in the tube lumen, which caused airway obstruction (adenotonsillectomy to facilitate future decannulation). Nine of 10 patients with postoperative respiratory distress had a preoperative AHI >10 episodes/h.
Statham et al, 2006 [115]	Retrospective, cohort study	III	2315 patients younger than 6 years who underwent adenotonsillectomy for OSAS. Children aged < 3 years (n=737) had a mean age of 2.25 ± 0.54 years and those aged 3-5 years (n=1578) had a mean age of 4.36 ± 0.85 years.	149 (6.4%) developed a postoperative respiratory complication. The prevalence of comorbid medical conditions was 58.3%: asthma (29.5%), history of prematurity (15.4%), obesity (13.4%), central nervous system conditions (7.3%), craniofacial malformations (4.0%), and a history of previous airway surgery

				(4.0%). Children younger than 3 years were at a greater risk for developing a postoperative respiratory complication compared with patients aged 3 to 5 years (9.8% vs 4.9%, P<0.001). Children younger than 3 years had a nearly 2-fold increased risk for postoperative respiratory complications (OR 1.98; 95% confidence interval, 1.41-2.77) after adjustment for race and gender. 60% of patients with respiratory complications required supplemental oxygen and the remaining subjects needed insertion of nasopharyngeal airway, re-intubation or CPAP.
Mitchell & Kelly, 2005 [116]	Prospective, cohort study	IV	20 children with OSAS (mean age 2.2 years; range 1.1-3 years; 75 % male) who underwent adenotonsillectomy; 80%	The mean preoperative respiratory distress index was 34.1 episodes/hand the mean postoperative respiratory disturbance

			of children had medical comorbidities: gastroesophageal reflux disease (n=9); asthma (n=8); obesity (n=6); Down syndrome (n=4); congenital heart disease (n=4); premature birth (n=3); allergic disease (n=2); cerebral palsy (n=1); and chromosomal abnormality (n=1).	index was 12.2 episodes/h (P <0.0001). After surgery, 7 (35%) children had a respiratory disturbance index <5 episodes/h. Thirteen (65%) had a postoperative respiratory disturbance index ≥5 episodes/h (persistent OSAS). Six (30%) children were hospitalised ≥4 days. Three (15%) children required an overnight stay in the intensive care unit. The most common reason for prolonged hospital stay was poor oral intake (6 children-30%). Two (10%) children had laryngospasm post-extubation and 1 of these children required reintubation. Five (25%) children required supplemental oxygen due to postoperative hypoxaemia.

Shatz et al, 2004 [105]	Retrospective, cohort study	IV	24 infants younger than 1 year with upper airway obstruction, obstructing adenoids and OSAS but no other abnormalities.	Presenting symptoms (including apnoea episodes), physical examination findings, and results of polysomnography, endoscopy, pHmetry, and echocardiography were reviewed. With careful preoperative and postoperative monitoring, all 24 infants underwent adenoidectomy without complications. All patients had marked improvement with complete resolution of upper airway obstruction symptoms, failure to thrive, and gastroesophageal reflux disease.
Greenfeld et al, 2003 [15]	Prospective, cohort study	IV	29 consecutive infants <18 months of age who underwent polysomnography (PSG) and were diagnosed with OSAS due to adenotonsillar hypertrophy	A paediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of OSAS symptoms post-treatment was collected.

				Two infants underwent adenoidectomy only and the rest of them had adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants. Other symptoms included: sleep apnoea (72%), frequent movements during sleep (69%), mouth breathing (62%) and recurrent awakenings (38%). Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$ percentile to the $42^{nd} \pm 32^{nd}$ percentile (P<0.001). 14/29 (48%) of the infants dropped two or more major percentiles prior to surgery. Following surgery, significant weight

					gain increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P<0.0001). 5/29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3/5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was documented in 6/23 (26%) of infants and repeat adenoidectomy was required.
Slovik et al, 2003 [117]	Retrospective, cohort study	IV		39 children aged 6 to 23 months (mean 15.9 ±4.9 months) who underwent adenotonsillectomy for OSAS	Comorbidities included: 4 patients had laryngomalacia, 2 patients had mild asthma, 4 patients were born prematurely (gestational age of 27-33 weeks), 2 patients had periventricular haemorrhage and bronchopulmonary

				dysplasia, 1 patient had pulmonary hypertension and 1 patient had a ventricular septal defect. All children were hospitalized postoperatively and were monitored by overnight pulse oximetry. There was marked improvement in nadir SpO_2 (pre-operative vs. postoperative values; $P<0.05$). Complications occurred in 7 children (20%) and 5 of them were older than 1 year. Complications included: bleeding (n=2; 5.7%); dehydration (n=3; 8.6%); hypercapnia (n=1; 2.9%); and laryngospasm (n=1; 2.9%).
Werle et al, 2003 [118]	Retrospective, cohort study	IV	94 children with age ranging from 12 to 23 months (mean age 19.6 ± 3.1 months) who underwent tonsillectomy and/or adenoidectomy	The indications for surgery were: included OSAS in 51 patients (54%), chronic or recurrent tonsillitis in 30 (32%), both OSAS and

				infection in 11 (12%), and acute tonsillitis with airway obstruction in two (2%). 50% of children had comorbid conditions: asthma, cardiac anomalies, seizure disorders, Down syndrome. Ten patients (11%) had a history of previous adenoidectomy. Eight children (8%) underwent preoperative polysomnography. Hospital stays ranged from 4 h to 16 days. Complications included haemorrhage in four patients (4%) and pneumonia in two (2%). Respiratory complications was managed with oxygen administration in 27 patients (29%), reintubation in 7 (7%), CPAP in 3 (3%), and nasopharyngeal airway placement in 3 (3%). Of the 88 patients on oral fluid, only five (5%) resumed oral intake later

				than 24 h postoperatively. Two patients (2%) experienced significant emesis after surgery. Four patients (4%) required treatment for dehydration after discharge.

5.4. What is the youngest age for adenotonsillectomy in children for OSAS related to adenotonsillar hypertrophy?

Author, year	Type of Study	Class	Subjects	Methods and findings
Robison et al, 2013 [99]	Retrospective, cohort study	III	295 infants diagnosed with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 montsh and with follow-up ≥6 months later.	OSAS was graded as mild (AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common interventions with average age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76 patients (20.9%, 12.8 months); supplemental

| | | | | oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16 patients (4.4%, 25.7 months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24 months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following intervention was highest after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP. The average ages at initiation of intervention were: observation, 12.8 months (range, 3–24 |

| | | | | months); supplemental oxygen, 11.7 months (range, 3–35 months); CPAP/BPAP, 15.6 months (range, 3–29 months); adenoidectomy, 17.7 months (range, 5–50 months); tonsillectomy, 25.7 months (range, 15–40 months); adenotonsillectomy, 22.3 months (range, 11–64 months); and tracheostomy, 15.3 months (range, 6–27 months). |
| Slovik et al, 2003 [117] | Retrospective, cohort study | IV | 39 children aged 6 to 23 months (mean 15.9 ±4.9 months) who underwent adenotonsillectomy for OSAS | Comorbidities included: 4 patients had laryngomalacia, 2 patients had mild asthma, 4 patients were born prematurely (gestational age of 27-33 weeks), 2 patients had periventricular haemorrhage and bronchopulmonary dysplasia, 1 patient had |

				pulmonary hypertension and 1 patient had a ventricular septal defect. All children were hospitalized postoperatively and were monitored by overnight pulse oximetry. There was marked improvement in nadir SpO_2 (pre-operative vs. postoperative values; $P<0.05$). Complications occurred in 7 children (20%) and 5 of them were older than 1 year. Complications included: bleeding (n=2; 5.7%); dehydration (n=3; 8.6%); hypercapnia (n=1; 2.9%); and laryngospasm (n=1; 2.9%).

5.5. What are the efficacy and risks of continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NPPV) for OSAS in young children?

a+b+c. *Efficacy, complications and interface*

Author, year	Type of Study	Class	Subjects	Methods and findings

Amaddeo et al, 2016 [119]	Retrospective, cohort study	IV	44 neonates with Pierre Robin sequence over a period of 1 year	i) Severe upper airway obstruction: inability to breathe spontaneously and maintain normoxia and normocapnia without invasive or noninvasive positive pressure ventilation; ii) moderate upper airway obstruction: AHI >10 episodes/h and or desaturation index >15 episodes/h and/or SpO_2 nadir <90% and/or maximum end-tidal carbon dioxide level >50 mHg (daytime nap polygraphy). In the severe upper airway obstruction group, CPAP was used for 24 h per day initially and over the next 1-2 weeks was progressively applied only during sleep periods. In the moderate upper airway obstruction group, CPAP was used only during sleep periods. The interface used was a nasal mask and the starting pressure was 6 cmH_2O

				which was increased rapidly to the required level. Tracheostomy was performed if patient was dependent on mechanical ventilation by endotracheal tube or CPAP treatment was not successful. 24 of 44 patients did not have upper airway obstruction. 9 of 44 patients had severe upper airway obstruction; 5 of them responded to CPAP and 4 required tracheostomy. 11 of 44 patients underwent polygraphy and 7 of them had a normal study. The rmaining 4 patients had AHI 19-42 episodes/h, desaturation index 18-137 episodes/h, SpO_2 nadir 78-90% and maximum end-tidal carbon dioxide 41-55 mmHg. All 9 patients with moderate-to-severe upper airway obstruction tolerated nasal CPAP and were discharged home

				after a median of 30 days (range 20-40 days). The required airway pressure was 6-8 cmH$_2$O. 5 of 9 infants were weaned off CPAP after 1-5.5 months and 4 of 5 were still on CPAP during the study (4 months).
Joseph et al, 2015 [120]	Case series		5 children aged 2 months to 15 years who were treated with high-flow nasal cannula for OSAS. Two of 5 children were younger than 24 months.	Patients had OSAS associated with hypotonia and/or craniofacial abnormalities but could not tolerate nCPAP. With the use of high-flow nasal cannula, mean AHI decreased from 22.98 episodes/h to 5 episodes/h (P = 0.034) and mean nadir SpO$_2$ increased from 65% to 81.4% (P = 0.011).
Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Robin sequence (1 y.o.)	10 (25.6%) infants had mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients or 74.4%) had severe OSAS (AHI >10

				episodes/h). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge. 30.0% of infants with mild/moderate OSAS were placed on continuous positive airway pressure during admission and 20.0% of infants at discharge. Amongst those with severe OSAS, 82.8% required airway interventions: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge. Infants with severe OSAS required tube feeding at discharge more frequently than infants with mild/moderate OSAS (89.7% vs 50.0%). Children were at lower weight centiles at

				discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Leonardis et al., 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40

				patients had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS. 68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy

				(7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration and blood transfusion in cases of prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale).

| | | | | Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%). |
| Chatwin et al., 2011 [121] | Case series | IV | 13 infants with spinal muscular atrophy-type 1 referred to a single centre | NPPV was provided for the following indications: CPAP flow driver dependency (n=3); nocturnal hypoventilation (n=3); to enable successful extubation (n=2); in anticipation of respiratory decompensation (n=3); oxygen dependency/ decompensation (n=2). Pectus excavatum (chest wall shape) improved with NPPV. Use of NPPV: just nocturnally (n=7); 24 |

				h/day (n=2); 23 h/day (n=1); 20 h/day (n=1); and 16h/day (n=2).
Wormald et al, 2009 [122]	Case series		6 infants with upper airway obstruction	CPAP/NPPV were applied to prevent tracheostomy in infants with severe laryngo-tracheomalacia and to optimise the timing of surgery in subglottic stenosis. They were also used to stabilise the airway following supraglottoplasty to manage OSAS.
Petrone et al, 2007 [123]	Case series	IV	9 infants (2-33 m.o.) with spinal muscular atrophy type 1 or 2	All patients underwent polygraphy for the assessment of the AHI, mean SpO_2, oxygen desaturation index, transcutaneous carbon dioxide tension ($TCpCO_2$), and mean phase angle during sleep as a measure of thoracoabdominal coordination. A second polygraphy was performed with use of NPPV. On

				NPPV, there was significant improvement in desaturation index, mean transcutaneous pCO_2 and phase angle (improved thoracoabdominal coordination). All patients used high-span bilevel PAP (IPAP minus EPAP range: 14–20 cm H_2O) to obtain adequate thoracic and alveolar expansion. Phase-angle improvement correlated with the bilevel PAP pressure.
Essouri et al, 2005 [124]	Retrospective, cohort study	IV	10 infants (5 female) with upper airway obstruction and age 3-18 months who were treated with CPAP or BPAP	50% of the patients had laryngomalacia; other patients had Pierre Robin sequence, tracheomalacia, tracheal hypoplasia, bronchomalacia or bronchopulmonary dysplasia. Positive pressure was applied using a nasal mask and a home ventilator. CPAP ranged from 8 to 12 cmH_2O. For

				BPAP the inspiratory pressure was 4 to 6 cmH_2O above the expiratory pressure. Both CPAP and BPAP were accompanied by a decrease in breathing rate and esophageal pressure swings.
Massa et al, 2002 [125]	Retrospective, cohort study	IV	66 children aged 0-19 years with OSAS who were considered for nCPAP treatment. 18 (27%) patients were younger than 1 year; 28 (42%) were aged 1 to 5 years; 12 (18.2%) were 6 to 12 years old and 8 (12.1%) were 13-19 years old.	Moderate-to-severe OSAS was defined as: i) obstructive apnoea index $\geq$5 episodes/h; and/or desaturation ($\geq$4% lasting >10 s) index $\geq$4 episodes/h and SpO_2 nadir <90%. 24 of 66 children had craniosynostosis, 8 had mucopolysaccharidosis, 6 had neuromuscular disease, 2 had Down syndrome and 3 had laryngotracheomalacia or bronchomalacia. nCPAP was started at 4 cmH_2O and titrated up by 2 cmH_2O until OSAS and oxyhaemoglobin

				desaturations resolved. 42 of 66 (63.6%) children tolerated nCPAP treatment. Follow-up clinical evaluations and sleep studies were performed at 1, 6 and 12 months to assess the efficacy of nCPAP, re-adjust airway pressure and the mask size. Patients used nCPAP for a period of 2 months to 6.5 years. Mean airway pressure was 8.5 cmH$_2$O (range 4-16 cmH$_2$O). Minor complications related to mask fit (eye or skin irritation) or nasal dryness were noted.
Downey et al, 2000 [126]	Retrospective, cohort study	IV	18 children with OSAS younger than 2 years.	All patients underwent polysomnography and CPAP trial for OSAS treatment. Patients were classified in 4 groups according to response to CPAP. Group 1: 2 of 6 children with

283

				tracheostomies used CPAP; group 2: 2 children without OSAS resolution after adenotonsillectomy who were treated with CPAP successfully and OSAS resolved over time; group 3: 4 patients who did not tolerate CPAP (one patient with obesity and hypothyroidism, 2 who required craniofacial surgery, one with laryngomalacia; and group 4: 6 patients who tolerated CPAP and progressively had OSAS resolution (one with laryngomalacia, one with bronchopulmonary dysplasia, one with Down syndrome, one with Pierre Robin sequence, one with OSAS and ALTE and one with congestive heart failure). Apnoea index decreased and SpO_2 nadir increased.
McNamara et al, 1999	Retrospective, cohort	IV	24 infants (9 female) with	Patients included in the

| [127] | study | | | OSAS aged 1-51 weeks | study had family history of SIDS, apparent life-threatening event, micrognathia, choanal atresia, laryngomalacia, Beckwith-Wiedemann syndrome, Smith-Lemli-Opitz syndrome or Moebius syndrome. Nasal CPAP treatment was initiated if the obstructive-mixed apnoea index was greater than 5 episodes/h. Initial pressure required was 3.7 to 6 cmH$_2$O. Both the obstructive apnoea index and desaturation index decreased significantly. The mean obstructive apnoea index was 43.6 ± 8.3 episodes/h in REM sleep and 14.6 ± 3.9 episodes/h in NREM sleep and decreased to 0.4 ± 0.1 episodes/h and 0.1 ± 0.1 episodes/h, respectively with CPAP (P <0.05). Clinical evaluation and polysomnography were repeated every 2-4 |

| | | | | months during the first year of life and every 6 months thereafter. 18 infants tolerated CPAP and were treated for 1month to 4.3 years. 5 infants, all with micrognathia or choanal atresia used CPAP for over 2 years with airway pressures between 6.5 and 10 cmH$_2$O. When nasal CPAP was initiated in these 5 infants, an average pressure of 4.6 $\pm$ 0.2 cm cmH$_2$O was required to prevent obstructive events; after 2 to 4.3 years the average pressure was increased to 7.7 $\pm$ 0.7 cmH$_2$O (P <0.05). In 13 infants (mostly those with history of apparent life-threatening events or family history of SIDS) OSAS resolved. |
| Guilleminault et al, 1995 [128] | Retrospective, cohort study | IV | 74 infants (39 girls) with SDB and narrow upper | Presenting symptoms were: apparent life- |

			airway who were treated with nasal CPAP (mean age 24 ± 9 weeks).	threatening event (n=17; 23%); failure to thrive (n=8; 11%); abnormal breathing pattern (n=49; 66%). 38 infants had syndromic conditions: Down syndrome (n=7); Pierre Robin (n=9); cleft palate (n=2); Treacher Collins (n=2); Hunter syndrome (n=1); achondroplasia (n=3); cerebral palsy (n=7); epilepsy with monoplegia (n=3); hemiplegia (n=2); unclassified muscle disorder (n=1); hydrocephalus with shunt (n=1). 57 (77%) had apparent or subtle craniofacial abnormalities (e.g. high-arched hard palate or small chin). 41.9% of patients had an AHI >25 episodes/h; 37.8% had an AHI 1-25 episodes/h; 9.5% had an AHI 5-10 episodes/h; and 10.8% had an AHI <5 episodes/h. 72 of 74

				infants were treated successfully with CPAP. Mean follow-up was 35 ±21 months. 28 (38.9%) patients eventually discontinued CPAP and 37 (51.4%) were still using CPAP at the time of the study.

5.6. What are the efficacy and risks of treatment interventions for OSAS related to specificic conditions?

5.6.a. Choanal atresia or nasal pyriform aperture stenosis

a. *Choanal atresia*

Author, year	Type of Study	Class	Subjects	Methods and findings
Durmaz et al, 2008 [129]	Case series and meta-analysis		238 cases with choanal atresia which was managed by transnasal endoscopic repair and were reported in 20 studies (age 2 days-53 years).	Follow-up period was 1-132 months. Surgical success rate was 85.3% and re-stenosis occurred in 14.7% of cases. One death was reported (0.4%) caused by intraoperative

				bleeding. Minor complications were noted in 14.2% of cases (mucosal bleeding, granulation tissue, minor synechiae, septal perforation, intranasal crusting).
b. *Nasal pyriform aperture stenosis*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Visvanathan et al, 2012 [73]	Case series		10 children who were diagnosed with nasal pyriform aperture stenosis	There were features of airway obstruction: persistent nasal congestion, tachypnoea, episodes of apnoea/cyanosis, poor feeding. Resistance was felt during passage of a nasogastric tube. All patients underwent craniofacial CT scan. 5 children were managed by nasal decongestants, humidification, nasopharyngeal airway insertion and management of laryngopharyngeal reflux. The remaining 5

				patients who did not respond to conservative management (i.e. worsening oxygen desaturations, recurrent episodes of apnoea/cyanosis and failure to thrive) were treated surgically. All infants who underwent surgery had bilateral pyriform aperture stenosis. A sublabial approach was used and excess bone was drilled away from the inferior inlet along the floor of the nose to the lateral process of the maxilla. Surgery was performed at an average age of 14 days (range 3–26 days).

5.6.b. Severe laryngomalacia				
Efficacy and risks of supraglottoplasty				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**

Czechowicz et al, 2015 [79]	Retrospective, cohort study	IV	76 children with laryngomalacia who underwent supraglottoplasty at age <2 years	Somatic growth changes from the time of surgery to an average of 9 months postoperatively were recorded. Body mass index increased from a mean of 15.4 kg/m^2 to 18.0 kg/m^2 and BMI percentile from a mean of 34th preoperatively to 51st postoperatively. The largest BMI percentile increases were recorded in infants that were 3 months old or younger at the time of supraglottoplasty, and in those under 12 months of age, who were in the lowest BMI quintile.
Durvasula et al, 2014 [85]	Retrospective, cohort study	IV	28 infants (≤12 months) and 26 children (>12 months) who underwent supraglottoplasty for severe laryngomalacia and were diagnosed with a neurologic condition (cerebral palsy, developmental delay,	Comparisons to 136 infants without comorbidities who underwent supraglottoplasty were carried out. Overall success rate of supraglottoplasty in the study population with

| | | | | Chiari I malformation, hydrocephalus, Dandy-Walker malformation) or syndromic comorbidity (including CHARGE, VATER, Down syndrome and others). | comorbidities was 67%. Neurologic conditions (P = 0.003) and syndromic comorbidities (P < 0.001) were associated with significantly reduced success rates when compared to the absence of comorbidities. Among children with inadequate response to surgical treatment (18 of 54 [33%]), 13% (7 of 54) required tracheostomy, 9% (5 of 54) needed CPAP (persistent OSAS), 7% (4 of 54) required a postoperative gastrostomy tube, and 4% (2 of 54) required revision of supraglottoplasty. Patients with cerebral palsy had significantly higher frequency of tracheostomy than those with other neurologic disorders (2 of 11 [18%] vs 0 of 20; P = 0.049). In infants, acute airway obstruction was the most common indication |

				for supraglottoplasty in the groups with neurologic disorders or syndromic comorbidities (success rates, 69% and 67%, respectively). In children, OSAS was the most common indication for surgery in the groups with neurologic disorders or syndromic comorbidities (success rates, 78% and 50%, respectively). Eleven infants (85%) and 14 children (78%) had preoperative dysphagia. Aspiration was identified by a videofluoroscopic swallow study or functional endoscopic evaluation of swallow, preoperatively in 8 of 8 infants (100%) and 6 of 14 children (43%) without gastrostomy tube. Five infants (38%) and 4 children (22%) presented preoperatively with a gastrostomy. In the majority of patients

				dysphagia resolved postoperatively.
Leonardis et al., 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40 patients had mild OSAS; 44 had moderate OSAS; and 42 had severe OSAS.

				68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy (7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other

				nonsurgical interventions were caffeine administration and blood transfusion in cases of prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale). Tracheostomy had a mean subjective score of 2.7. For patients who had

					both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%).
Powitzky et al, 2011 [32]	Retrospective, cohort study	III		20 infants (<1 y. o.) who underwent supraglottoplasty for severe laryngomalacia (failure to thrive or signs of severe respiratory distress, such as cyanotic spells, severe intercostal retractions, or prolonged apnoeas with significant desaturations while awake) or moderate laryngomalacia (stridor and associated retractions or dysphagia).	Patients underwent polysomnography pre- and post-supraglottoplasty. Outcome measures included changes in stridor, SDB, swallowing, and polysomnography parameters before and after surgery. Statistically significant improvements were demonstrated 1.1-5.8 months postoperatively in median AHI (-6.4 episodes/h; P=0.02).
O' Connor et al , 2009 [34]	Retrospective, cohort study	IV		10 children with moderate-to-severe	Polysomnography was performed before and after

			laryngomalacia who underwent supragtottoplasty with mean age at first presentation of 2 months and 19 days (range 30–134 days)	surgery. The mean time from preoperative polysomnography to supraglottoplasty was 12.1 days and from supraglottoplasty to post-operative polysomnography 83.2 days. The observed anatomical abnormalities were: short aryepiglottic folds (10/10 patients); prolapsing arytenoid mucosa (9/10); and prolapsing or omega-shaped epiglottis (4/10). Total sleep time increased from a mean of 382 min to 475 min (P=0.049) and SpO_2 from a mean of 74.8% to 87.6% (P=0.006); obstructive AHI decreased from a mean of 42.7 episodes/h to 4.47 episodes/h (P=0.009) and respiratory disturbance index from 49.9 episodes/h to 8.36 episodes/h (P=0.002), following

				supraglottoplasty. A non-significant improvement in mean transcutaneous carbon dioxide ($TcCO_2$) partial pressure occurred (from 57.1 mmHg to 52.8 mmHg) (P=0.259).
Zafereo et al, 2008 [35]	Retrospective, case cohort	IV	Ten infants with laryngomalacia and OSAS who underwent supraglottoplasty.	All 10 patients were extubated after the procedure and there were no peri- or postoperative complications. Postoperative nocturnal polysomnography was performed at 11 weeks postoperatively (range 2-29 weeks). Caregivers reported mild improvement (10%), significant improvement (70%), and complete resolution (20%) of stridor and snoring at 4 weeks after discharge. Marked improvements and statistically significant improvements were recorded in obstructive

				apnoea index, obstructive AHI, respiratory disturbance index and oxygen saturation of haemoglobin nadir (P <0.05).
Valera et al, 2006 [36]	Case series	IV	7 children with mean age 6.8 months (range 1-15 months) with severe laryngomalacia based on symptoms and flexible endoscopy	Four of the 7 children had a history of stridor; in 3 patients without stridor the predominant symptom of upper airway obstruction was snoring. There was history of cyanosis on effort and increased nocturnal work of breathing or apnoea. Baseline polysomnography was performed and subsequently patients underwent epiglottoplasty with bilateral incision of the aryepiglottic folds, followed by bilateral excision of excess mucosa in the lateral arytenoid region. If epiglottis had a posterior position,

				epiglottopexy was carried out. Polysomnography was repeated postoperatively. Preoperatively, one of 7 patients had moderate OSAS and the remaining children had severe OSAS and all of them had paradoxic breathing; respiratory disturbance index was 5.4 to 22.8 episodes/h (mean $\pm$ SD: 11.66 ± 7.51 episodes/h); minimum SpO_2 was 70% to 94% (mean $\pm$ SD: $81.71\% \pm 8.47\%$). Two of 7 patients with pharyngolaryngomalacia did not tolerate extubation and required tracheostomy. Of the remaining patients, 4 had marked improvement of respiratory symptoms and one only partial improvement of apnoea and stridor; 2 patients with feeding difficulties did not require a nasogastric tube postoperatively. At an

				average of 82 days after surgery, respiratory disturbance index decreased from a mean of 10 episodes/h preoperatively to a mean of 2.2 episodes/h (P <0.05); minimum SpO_2 tended to increase from 83.2% preoperatively to 86.4% postoperatively (P=0.07). Resolution of OSAS (respiratory disturbance index <1 episode/h) was not achieved in 3 patients with additional abnormalities: tracheomalacia; marked neurologic deficit; hypertrophy of the pharyngeal and palatine tonsils.
Durvasula et al, 2004 [85]	Retrospective, cohort study	IV	28 infants (≤12 months) and 26 children (>12 months) who underwent supraglottoplasty for severe laryngomalacia and were diagnosed with a	Comparisons to 136 infants without comorbidities who underwent supraglottoplasty were carried out. Overall

				neurologic condition (cerebral palsy, developmental delay, Chiari I malformation, hydrocephalus, Dandy-Walker malformation) or syndromic comorbidity (including CHARGE, VATER, Down syndrome and others).	success rate of supraglottoplasty in the study population with comorbidities was 67%. Neurologic conditions (P = 0.003) and syndromic comorbidities (P < 0.001) were associated with significantly reduced success rates when compared to no comorbidities. Among children with inadequate response to surgical treatment (18 of 54 [33%]), 13% (7 of 54) required tracheostomy, 9% (5 of 54) needed CPAP (persistent OSAS), 7% (4 of 54) required a postoperative gastrostomy tube, and 4% (2 of 54) required revision of supraglottoplasty. Patients with cerebral palsy had significantly higher frequency of tracheostomy than those with other neurologic disorders (2 of 11 [18%] vs 0 of 20; P =

				0.049). In infants, acute airway obstruction was the most common indication for supraglottoplasty in the groups with neurologic disorders or syndromic comorbidities (success rates, 69% and 67%, respectively). In children, OSAS was the most common indication for surgery in the groups with neurologic disorders or syndromic comorbidities (success rates, 78% and 50%, respectively). Eleven infants (85%) and 14 children (78%) had preoperative dysphagia. Aspiration was identified by a videofluoroscopic swallow study or functional endoscopic evaluation of swallow, preoperatively in 8 of 8 infants (100%) and 6 of 14 children (43%) without gastrostomy tube. Five infants (38%) and 4 children (22%) presented

				preoperatively with a gastrostomy.
Denoyelle et al, 2003 [130]	Retrospective, cohort study	IV	136 children, aged 3 days to 60 months (median age, 3 months) who underwent laser or instrumental bilateral supraglottoplasty.	102 children, aged 3 days to 19 months had isolated laryngomalacia; 34 children, aged 3 weeks to 60 months had additional congenital anomalies. Inadequate response to treatment (persistence of dyspnoea, sleep apnoea, failure to thrive, need for additional treatment) occurred in 12 (8.8%) of 136 cases, all of them having additional congenital anomalies. The overall rate of complications (granuloma, edema, small web, supraglottic stenosis) was 7.4% (10/136). There were no significant differences between the groups with isolated laryngomalacia or with co-existing congenital anomalies regarding the rate of

				recurrence requiring revision surgery (3/102, 2.9% vs. 3/34, 9%), the rate of minor complications (4/102, 3.9% vs. 1/34, 3%), or the rate of supraglottic stenosis (4/102, 3.9% vs. 1/34, 3%). Supraglottic stenosis was managed by revision surgery in 4 patients and/or noninvasive ventilation in 2 cases. The long-term outcome appeared to be better when reintervention could be avoided or was minimal.
Roger et al, 1995 [39]	Retrospective, cihort study	IV	985 children who underwent upper airway endoscopy for laryngomalacia.	115 (11.6%) children had epiglottoplasty endoscopically. Median age at surgery was 3.6 months (range: 8 days to 4 years); 77% of patients were younger than 6 months. OSAS was demonstrated in 11.3% of patients. The average time

				of postoperative follow-up was 30 months. Complete resolution of symptoms was noted in 53% of cases. Among 50 patients who underwent blood gas analysis before and after surgery: 58% had normalization of both oxygenation and ventilation; 22% had normalization of one parameter and improvement of the other; and 20% had improvement of both parameters without normalization.
Marcus et al, 1990 [40]	Retrospective, cohort study	IV	6 patients with severe laryngomalacia who underwent epiglottoplasty at the age of 10.3 ± 5.3 (SEM) months.	4 patients had history of life-threatening episodes of airway obstruction prior to surgery (2 underwent endotracheal intubation; 1 required cardiopulmonary resuscitation; 2 had failure to thrive and 2 were diagnosed with cor pulmonale). Polysomnography was

				performed during a daytime nap both before and after epiglottoplasty. Preoperatively, 6 children had OSAS, 4 had hypoxaemia ($SpO_2 <90\%$ while breathing room air), and 4 had hypoventilation (end-tidal carbon dioxide pressure >45 mm Hg). Postoperatively, patients were intubated for 25 ± 7 hours and were discharged after 4 ± 1 days. Follow-up polysomnography was performed 2.8 ± 1.0 months after surgery and was improved in all patients; 2 patients had residual, mild episodes of obstructive sleep apnoeas, and 1 patient had mild hypoventilation and desaturation. Life-threatening events did not occur in any patients and no further hospitalisations were required.

5.6.c. Syndromic craniosynostosis with or without midface hypoplasia?				
a+b+c. *Nasopharyngeal airway, adenotonsillectomy, nCPAP, midface advancement*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was repeated within 3–6 months. OSAS was defined as obstructive AHI ≥ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if

				AHI 5–24 episodes/h; and severe if AHI ≥25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. The majority of patients underwent cranial vault remodeling before the age of 1 year. Treatment for OSAS was offered at a median age of 4.5 years (range 4 months-18 years old). Adenotonsillectomy was the most frequent intervention (n=20) followed by transverse widening of the hypoplastic maxilla with a hyrax expander (n=1),

				midface advancement (n=6), tracheostomy (n=3) or ventilation (n=2). A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.
Mitsukawa et al, 2013 [131]	Retrospective, cohort study		11 children with syndromic craniosynostosis and OSAS (4 with Crouzon syndrome; 3 with Pfeiffer syndrome and 4 with Apert syndrome). Ages ranged from 7 months to 3 years and 9 months (mean age 2 years and 5 months).	Midfacial distraction was performed using an internal or external device to improve OSAS and to avoid tracheostomy. Participants underwent pre- and postoperative (12-18 months) polysomnograms and cephalograms. Polysomnograms and cephalograms improved markedly all patients

				avoided tracheostomy. the area of the maxilla increased from 22.1 to 34.4 cm^2
Ahmad et al, 2012 [132]	Retrospective, cohort study	IV	12 children younger than 30 months with severe syndromic craniofacial dysostosis who underwent monobloc frontofacial advancement with a rigid external distractor frame (mean age, 18 months; range 4-30 months).	One child had Apert syndrome, 6 had Crouzon syndrome and 5 had Pfeiffer syndrome. All participants had moderate-to-severe upper airway obstructions as demonstrated by polysomnography. 9 patients had tracheostomy prior to craniofacial surgery and 3 had tracheostomy to secure a patent airway for the operation; 8 had raised intracranial pressure. All patients underwent frontofacial monobloc surgery by distraction osteogenesis using a rigid, external distractor frame. Mean follow-up postoperatively was 25 months (range 6 months to

				5 years). 7 patients were decannulated. Raised intracranial pressure resolved in all cases. Two children had cerebrospinal fluid leak (meningitis in one case). Three cases of pin-site infections required treatment with topical and/or systemic antibiotics. Two children had the rigid external distraction frame repositioned and one patient died 9 months later following a tracheal reconstruction procedure.
Coeugniet et al, 2012 [133]	Retrospective, cohort study	IV	17 children with craniosynostosis and midface retrusion (10 boys and 7 girls; mean age at the time of surgery 34.4 months; range 7 to 120 months); 7 of 17 patients were younger than 24 months.	In 8 patients with significant periods of sleep apnoea (pO_2 <90 mmHg; pCO_2 >45 mm Hg) preoperatively, postoperative polysomnography was normal. Six patients, who did not undergo polysomnography had snoring preoperatively

				which resolved postoperatively. Three patients did not have any respiratory symptoms preoperatively.
Ahmed et al, 2008 [134]	Retrospective, cohort study	IV	27 children with syndromic craniofacial synostosis (10 patients with Crouzon syndrome; 12 with Apert syndrome; 4 with Pfeiffer syndrome; and 1 Saethre-Chotzen syndrome) who underwent nasopharyngeal airway insertion at mean age 12.3 months (range 0.5 to 48 months).	6 of 27 patients, 6 had adenoid hypertrophy and underwent adenoidectomy by suction diathermy prior to nasopharyngeal airway insertion. Based on clinical monitoring and nocturnal oximetry, 17 children had severe OSAS and 10 children had moderate OSAS. After airway insertion, 3 subjects had moderate and 24 had mild OSAS. After tube placement, there was improvement in nocturnal mean SpO_2, oxygen desaturation index and % time with SpO_2 <90%.
Massa et al, 2002 [125]	Retrospective, cohort study	IV	66 children aged 0-19 years with OSAS who	Moderate-to-severe OSAS was defined as: i)

			were considered for nCPAP treatment. 18 (27%) patients were younger than 1 year; 28 (42%) were aged 1 to 5 years; 12 (18.2%) were 6 to 12 years old and 8 (12.1%) were 13-19 years old.	obstructive apnoea index ≥ 5 episodes/h; and/or desaturation ($\geq 4\%$ lasting >10 s) index ≥ 4 episodes/h and SpO_2 nadir $<90\%$. 24 of 66 children had craniosynostosis, 8 had mucopolysaccharidosis, 6 had neuromuscular disease, 2 had Down syndrome and 3 had laryngotracheomalacia or bronchomalacia. nCPAP was started at 4 cmH_2O and titrated up by 2 cmH_2O until OSAS and oxyhaemoglobin desaturations resolved. 42 of 66 (63.6%) children tolerated nCPAP treatment. Follow-up clinical evaluations and sleep studies were performed at 1, 6 and 12 months to assess the efficacy of nCPAP, re-adjust airway pressure and the mask size. Patients used nCPAP for a period of 2 months to 6.5 years.

				Mean airway pressure was 8.5 cmH$_2$O (range 4-16 cmH$_2$O). Minor complications related to mask fit (eye or skin irritation) or nasal dryness were noted.

5.6.d. Severe mandibular hypoplasia (e.g. Pierre Robin sequence)

a+ b + c. *Prone positioning, nasopharyngeal tube insertion, orthodontic appliance, glossopexy, nCPAP, NPPV*

Author, year	Type of Study	Class	Subjects	Methods and findings
Buchenau et al, 2017 [135]	Retrospective, cohort study	IV	122 infants with isolated and 85 infants with syndromic Robin sequence aged 4-42 days on admission	Median mixed obstructive apnoea index at baseline was 8.8 (range 2.1–19.7) episodes/h. 55 (45%) infants had severe OSAS (mixed obstructive apnoea index >10 episodes/h). Mixed obstructive apnoea index was significantly decreased at discharge and 3 months later. None of them required mechanical ventilation or tracheostomy. A nasogastric feeding tube

				was necessary in 66% of cases on admission and in 8% of cases at discharge. Weight improved from a median z-score −0.7 (−1.39 to −0.24) at admission to −0.5 (−0.90 to +0.02) at 3 months after discharge (P=0.021). The most frequent side effect was tender spots on the hard or soft palate.
Paes et al, 2015 [136]	Retrospective, cohort study	IV	75 infants with Robin sequence aged <1 year	43% of infants had isolated Robin sequence. Mean follow-up was 7.4 years (1-17 years). 59% of infants were managed conservatively i.e. side/prone positioning, temporary oxygen supplementation, CPAP, nasopharyngeal tube. 41% of infants were treated with tongue-lip adhesion or mandibular distraction osteogenesis. A tracheostomy was performed if the tongue-

| | | | | | lip adhesion failed or there was subglottic obstruction. Children were decannulated after an average of 13.4 months (range 4.1–36.5 months). 77% of infants required temporary nasogastric tube feedings. Six infants (8 %), all syndromic Robin sequence died due to cardiac or respiratory pathology at a mean age of 416 days (44 days– 3 years). |
| Rathe et al, 2015 [44] | Retrospective, cohort study | IV | 48 infants with Pierre Robin sequence treated over an 11-year period | 14.6% of infants had syndromic Pierre Robin sequence.62.5% of patients had upper airway obstruction. Polysomnography was performed in 30 infants: 53.3% had obstructive and/or central apnoeas. Overall fatality rate was 10.4% and fatality due to upper airway obstruction was 2%. Prone positioning |

					was applied in 43.8% of patients; NPPV in 16.7% of infants; nasopharyngeal or oropharyngeal airway in 20.9%; endotracheal intubation in 18.8%; tracheostomy in 8.3%; glossopexy in 2.1%; and mandibular distraction osteogenesis in 2.1%.
van Lieshout et al, 2014 [45]	Retrospective, cohort study		IV	59 infants with Robin sequence born between 2000-2010 (49% females; age < 1 year)	61% of patients had isolated Robin sequence; 14% had syndromic Robin sequence (Treacher Collins syndrome, Stickler syndrome, Nager syndrome, Miller syndrome, Trisomy 19, chromosome 11 duplication-12(q23,3:q24,3) deletion); 25% had associated abnormalities without a diagnosed syndrome (hypertelorism, microtia, etc.). Most patients underwent upper airway endoscopy and/or

				polysomnography. An obstructive AHI <1 episode/h was considered normal, 1-5 episodes/h as mild OSAS, 5-24 episodes/h as moderate OSAS, and >24 episodes/h severe OSAS. 42 of 59 (71.2%) subjects had one or more sleep studies: 7.1% of patients had mild OSAS;7.1% had moderate OSAS; and 19% had severe OSAS. 12 of 42 children underwent upper airway endoscopy: in 6 of 12 patients the tongue base was placed against the posterior pharyngeal wall. 69.5% of 59 children were managed with prone positioning only; 10.2% initially were placed in the prone position but subsequently required oxygen administration, nasopharyngeal airway insertion, CPAP or mandibular distraction osteogenesis (1 case). 4 of

				59 (6.8%) patients required endotracheal intubation in the neonatal period which was followed by tracheostomy and in one case the tracheostomy was followed by mandibular distraction osteogenesis. The remaining 8 patients were managed by intubation (one case), oxygen administration, nasopharyngeal airway insertion or CPAP followed in 4 cases by mandibular distraction osteogenesis. 47% of infants were supported by nasogastric or gastrostomy tube feedings. 3 (5%) patients died.
Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Robin sequence (1 y.o.)	10 (25.6%) infants had mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients or 74.4%) had severe OSAS (AHI >10

				episodes/h). 24 (61.5%) had other abnormalities: Stickler syndrome (n=7), chromosomal abnormalities (n=4), dysmorphic or syndromic features (n=7), cardiac abnormalities (n=4). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge. 30.0% of infants with mild/moderate OSAS were placed on continuous positive airway pressure during admission and 20.0% of infants at discharge. Amongst those with severe OSAS, 82.8% required airway interventions as an inpatient, 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge.

				Infants with severe OSAS required tube feeding at discharge more frequently than infants with mild/moderate OSAS (89.7% vs 50.0%). Children were at lower weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score was 4. The presence of obstructive events and increased work of breathing was used to re-classify UAO severity if necessary. When UAO was mild, the child had a

				trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. The average duration of hospitalization after nasopharyngeal airway insertion was 10 days (range 6–28 days). For infants discharged with an artificial airway, the immediate post-insertion sleep study revealed no

				UAO in 7.9% of cases, mild UAO in 61.9% and moderate UAO in 30.2%. The average duration of nasopharyngeal airway use was 8 months (3 weeks to 27 months); 88.9% of infants had the nasopharyngeal airway removed before the age of 12 months. Of patients who required tracheostomy, 64.2% were decannulated at a median age of 3 years (range 2-5 years), whereas the remaining subjects continued to have tracheostomy or underwent mandibular distraction osteogenesis surgery. 82/104 (78.8%) infants required feeding with a nasogastric tube for a few weeks to months. No fatalities related to UAO were reported.

Meyer et al, 2008 [137]	Retrospective, cohort study	IV	74 children with Pierre Robin sequence with a median age of 6 months (range 0-11.5 years); 53 with isolated Pierre Robin sequence and 21 with syndrome or neurologic comorbidity.	The main outcomes for efficacy of interventions were CO_2 partial pressure in capillary blood and oxygen saturation of haemoglobin. 49% of patients required no airway interventions or responded to prone positioning; 19% of children were managed with a nasopharyngeal airway; 32% of patients required mandibular distraction osteogenesis, tracheostomy or tracheostomy followed by mandibular distraction osteogenesis.75% of patients who required surgical treatment did not respond to a trial of nasopharyngeal airway insertion. 51% of children were fed by nasogastric tube, 19% by gastrostomy tube and 30% had initially a nasogastric tube which was replaced by a gastrostomy tube.

Buchenau et al, 2007 [138]	Randomised clinical trial with cross-over disign	II	11 infants with isolated Pierre Robin sequence, aged 0-60 days and with mixed obstructive apnoea index >3 episodes/h were recruited.	Infants were allocated to insertion of palatal plate without velar extension followed by insertion of palatal plate with velar extension or vice versa. Each device was used for at least 36 h. Polysomnography was performed at baseline and after insertion of each device. The geometric mean of mixed obstructive apnoea index was 13.8 (7.5–25.4) episodes/h at baseline, 14.8 (5.4–41.0) after the palatal plate without extension (P=0.84) and 3.9 (1.6–9.5) after the palatal plate with velar extension (P<0.01).
Denny et al, 2004 [139]	Retrospective, cohort study	IV	11 infants with Pierre Robin sequence aged 2-6 weeks who underwent tongue-to-lip adhesion	Patients were followed for an average period of 7.9 years (range 5-15 years). The procedure was successful in maintaining airway patency in 8 of 11

				patients (73%). Of the 3 children who did not improve: 1 had repeat tongue-to-lip adhesion; and 2 had mandibular distraction osteogenesis. Of the 8 patients with good response: 2 had mandibular distraction osteogenesis; and 1 underwent tracheostomy and then mandibular distraction osteogenesis to improve airway patency. Two additional children had distraction osteogenesis for orthodontic purposes. 6 of 11 (54.5%) patients had gastrostomy placement for feeding purposes.
Schaefer et al, 2004 [50]	Retrospective, cohort study	IV	21 patients with isolated Pierre Robin sequence treated by one surgeon over a 9-year period; 18 of 21 infants presented during the first week of life; 3 other infants were	Patients were followed for a median period of 33 months (range 9-70 months). Airway patency was achieved with prone positioning for 10 (47.6%) patients, with tongue-lip

				12-33 months old	adhesion for 7 of 10(47.6%) patients who underwent the procedure, with tracheostomy for 2 (9.5%) patients, and with mandibular distraction osteogenesis for 3(14.3%) patients. There was significant change in the maxillary-mandibular discrepancy during the first 1 year of life (P <0.0001). Oromotor studies performed ≥3 months after reversal of tongue-lip adhesion reversal (n = 9) demonstrated no deficits in tongue function, relative to other children with cleft lips/palates.
Hoffman, 2003 [140]	Retrospective, cohort study		IV	23 infants with Pierre Robin sequence (7 non-syndromic) aged 4-115 days with respiratory distress, episodes of hypoxaemia and/or obstructive sleep apnoea	All patients underwent tongue-lip plication. Preoperatively, mean SpO$_2$ nadir was 63.2 ± 17.1%, which improved to 88.3 ± 12.9% after the third postoperative day

				in sleep studies.	(P= 0.0005). The mean highest carbon dioxide level was 57.5 ± 19.4 torr before surgery and 52.9 ± 15.1 torr after surgery (P= 0.41). After surgery 10 infants were weaned to bottle-feeding alone, 4 infants were discharged with gastrostomy tubes and 9 infants were discharged home with nasogastric tubes. Of these patients, 5 infants later converted to oral feeding, one was lost to follow-up, and 3 underwent gastrostomy because of myopathy (1), aspiration on swallow study (1), and severe oral aversion (1). The 7 infants with gastrostomy tubes had associated congenital malformations or syndromes. All patients with isolated Pierre Robin sequence were fed orally.

Kirschner et al, 2003 [141]	Retrospective, cohort study	IV	107 infants (60 female) meeting the criteria for Pierre Robin sequence over a 28-year period	74 (69.2%) were successfully managed by positioning alone. Surgical management of the airway was performed in the remaining 33 (30.8%) patients, 29 of whom underwent tongue-to-lip adhesion and 4 underwent tracheostomy. Dehiscence of the adhesion occurred in 5 patients (17.2%), two of whom required tracheostomy. Within the group of infants who underwent mucosal adhesion alone, the dehiscence rate was 41.6%. When the adhesion included muscular sutures, however, dehiscence occurred in none of the patients. Of the 24 patients in whom primary tongue-to-lip adhesion healed uneventfully, airway obstruction was successfully relieved in 20 (83.3%). Failure of a healed tongue-to-lip

| | | | | adhesion to relieve the airway obstruction resulted in tracheostomy (n=4). 6 patients who underwent tongue-to-lip adhesion (20.7%) ultimately required a tracheostomy; 5 of these patients (83.3%) were syndromic. Of patients requiring preoperative intubation, 42.9% ultimately required tracheostomy. |
| Li et al, 2002 [107] | Retrospective, cohort study | IV | 110 children with Pierre Robin sequence (64 with cleft palate) over 10 years; 85% of patients ≤3 months old | Prone posturing was effective in the treatment of mild airway obstruction in 82 (74.5%) patients with noisy breathing. 28 (25.5%) infants were intubated for severely increased work of breathing (maximum duration 3 weeks); 7 (6.4% of total cases) had a tongue-to-lip adhesion and 3 of them had relief of upper airway obstruction, |

				whereas in the other 4. rupture of the wound occurred and they underwent tracheostomy; 2 additional patients had tracheostomy without any other intervention; patients with tracheostomy were decannulated successfully. One of 2 patients who had insertion of a nasopharyngeal tube was relieved temporarily. 46 (41.8%) patients required nasogastric tube feeding; none of the patients required gastrostomy.
Marques et al, 2001 [109]	Prospective, cohort study	IV	62 infants with Pierre Robin sequence aged <6 m.o.; 53.2% of infants had isolated Pierre Robin sequence	All patients underwent nasopharyngoscopy. Upper airway obstruction was classified in 4 types according to Sher et al (1992). 75.8% of infants (90.9% of those with isolated Pierre Robin sequence) had type 1 obstruction; 12.9% type 2 obstruction; 6.5% type 3

				obstruction; and 4.8% type 4 obstruction. Response to treatment was defined as good pulmonary ventilation, reduced work of breathing and apnea, oxygen saturation of hemoglobin >90% and tolerance of oral feeding. Prone positioning or nasopharyngeal airway insertion were adequate interventions in 76.6% and 50% of patients with type 1 or type 2 obstruction, respectively; 14.5% of infants with type 1 obstruction underwent glossopexy. The remaining infants and 100% of those with type 3 or type 4 obstruction required tracheostomy (overall frequency of tracheostomy 20.9%). Overall fatality rate was 11.3%.
Gilhooly et al, 1993 [142]	Retrospective, cohort	IV	15 infants with Robin	2 infants who had severe,

	study			sequence and appreciable episodes of airway obstruction during sleep evaluated over a 3-year period for potential tongue-lip adhesion.	clinically apparent events of upper airway obstruction underwent tongue-lip adhesion without polysomnography. The remaining 13 infants underwent polysomnography; 7 of them did not have severe events and were discharged. 6 infants had clinically significant events of upper airway obstruction and tongue-lip adhesion was performed. On repeat polysomnography after successful tongue-lip adhesion did not demonstrate any clinically significant events.
Sher et al, 1992 [51]	Retrospective, cohort study	IV	53 infants with Robin sequence aged 1 day to 9 months.	All infants underwent nasopharyngoscopy and type of obstruction was classified according to Sher et al, 1986: Type I obstruction in 58.5% of infants; type II

				in 20.8%; type III in 9.4%; and type IV in 9.4% of infants. 48 (90.6%) patients responded well to insertion of nasopharyngeal tube. 24 infants (all with type I obstruction) underwent glossopexy. 7 infants with pharyngeal obstruction types II-IV who did not respond to insertion of nasopharyngeal tube required tracheostomy.
Sher et al, 1986 [52]	Retrospective, cohort study	IV	33 patients with craniofacial abnormalities and upper airway obstruction with ages 0 to 24 years.	Patients underwent polysomnography, nasopharyngoscopy and cephalometry. Obstruction at the oropharyngeal level was classified in 4 categories: posterior movement of the tongue towards the posterior pharyngeal wall; compression of the soft palate on the posterior pharyngeal wall by the tongue; collapse of the

				lateral pharyngeal walls; circular constriction of the pharynx. Nasopharyngeal tube, glossopexy, mandibular advancement or tracheostomy were selected based on endoscopic findings.
Cogswell et al, 1974 [77]	Case report		5 week-old infant with micrognathia, cleft palate, stridor, feeding difficulties and episodes of cyanosis	Clinical findings and ECG consistent with cor pulmonale. Biventricular hypertrophy was present. Persistent cyanosis was present and hypercapnia was detected in capillary blood specimens. Airway resistance was measured in different postures. Transthoracic pressure swings were recorded with an esophageal balloon and airflow and tidal volume were recorded using a pneumotachograph placed on a face mask. In the prone position, tidal volume were maximised and esophageal pressure

				swings were minimized.

d. *Nasogastric or gastrostomy tube feedings*

Author, year	Type of Study	Class	Subjects	Methods and findings
van Lieshout et al, 2014 [45]	Retrospective, cohort study	IV	59 infants with Robin sequence born between 2000-2010 (49% females; age < 1 year)	61% of patients had isolated Robin sequence; 14% had syndromic Robin sequence (Treacher Collins syndrome, Stickler syndrome, Nager syndrome, Miller syndrome, Trisomy 19, chromosome 11 duplication); 25% had associated abnormalities without a diagnosed syndrome (e.g. hypertelorism, microtia). Most patients underwent upper airway endoscopy and/or polysomnography. An obstructive AHI <1 episode/h was considered normal, 1-5 episodes/h as mild OSAS, 5-24 episodes/h as moderate OSAS, and >24 episodes/h as severe OSAS. 42 of 59 (71.2%) subjects had one

				or more sleep studies: 7.1% of patients had mild OSAS; 7.1% had moderate OSAS; and 19% had severe OSAS. 12 of 42 children underwent upper airway endoscopy: in 6 of 12 patients the tongue base was placed against the posterior pharyngeal wall. 69.5% of 59 children were managed with prone positioning only; 10.2% initially were placed in the prone position but subsequently required oxygen administration, nasopharyngeal airway insertion, CPAP or mandibular distraction osteogenesis (1 case). 4 of 59 (6.8%) patients required endotracheal intubation in the neonatal period which was followed by tracheostomy and in one case the tracheostomy was followed by mandibular

				distraction osteogenesis. The remaining 8 patients were managed by intubation (one case), oxygen administration, nasopharyngeal airway insertion or CPAP followed in 4 cases by mandibular distraction osteogenesis. 47% of infants were supported by nasogastric or gastrostomy tube feedings. 3 (5%) patients died.
Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score was 4. The presence of obstructive events and increased work of breathing was used to re-classify UAO severity if necessary. When UAO

				was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. The average duration of hospitalisation after nasopharyngeal airway insertion was 10 days (range 6–28 days). For infants discharged with an artificial airway,

				the immediate post-insertion sleep study revealed no UAO in 7.9% of cases, mild UAO in 61.9% and moderate UAO in 30.2%. The average duration of nasopharyngeal airway use was 8 months (3 weeks to 27 months); 88.9% of infants had the nasopharyngeal airway removed before the age of 12 months. Of patients who required tracheostomy, 64.2% were decannulated at a median age of 3 years (range 2-5 years), whereas the remaining subjects continued to have tracheostomy or underwent mandibular distraction osteogenesis surgery. 82 of 104 (78.8%) infants required feeding with a nasogastric tube for a few weeks to months. No fatalities related to UAO were

				reported.
Meyer et al, 2008 [137]	Retrospective, cohort study	IV	74 children with Pierre Robin sequence with a median age of 6 months (range 0-11.5 years); 53 with isolated Pierre Robin sequence and 21 with syndrome or neurologic comorbidity.	The main outcomes for efficacy of interventions were CO_2 partial pressure in capillary blood and oxygen saturation of haemoglobin. 49% of patients required no airway interventions or responded to prone positioning; 19% of children were managed with a nasopharyngeal airway; 32% of patients required mandibular distraction osteogenesis, tracheostomy or tracheostomy followed by mandibular distraction osteogenesis. 75% of patients who required surgical treatment did not respond to a trial of nasopharyngeal airway insertion. 51% of children were fed by nasogastric tube, 19% by gastrostomy tube and 30% had initially

				a nasogastric tube which was replaced by a gastrostomy tube.
Li et al, 2002 [107]	Retrospective, cohort study	IV	110 children with Pierre Robin sequence (64 with cleft palate) over 10 years; 85% of patients ≤3 months old	Prone posturing was effective in the treatment of mild airway obstruction in 82 (74.5%) patients with noisy breathing. 28 (25.5%) infants were intubated for severely increased work of breathing (maximum duration 3 weeks); 7 (6.4% of total cases) had a tongue-to-lip adhesion and 3 of them had relief of upper airway obstruction, whereas in the other 4. rupture of the wound occurred and they underwent tracheostomy; 2 additional patients had tracheostomy without any other intervention; patients with tracheostomy were decannulated successfully. One of 2 patients who had insertion of a

				nasopharyngeal tube was relieved temporarily. 46 (41.8%) patients required nasogastric tube feeding; none of the patients required gastrostomy.

Question 5.6.e. What are the efficacy and risks of mandibular distraction osteogenesis for OSAS in young children?

a + b. *Efficacy and complications*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
van Lieshout et al, 2014 [45]	Retrospective, cohort study	IV	59 infants with Robin sequence born between 2000-2010 (49% females; age < 1 year)	61% of patients had isolated Robin sequence; 14% had syndromic Robin sequence (Treacher Collins syndrome, Stickler syndrome, Nager syndrome, Miller syndrome, trisomy 19, chromosome 11 duplication); 25% had associated abnormalities without a diagnosed syndrome (hypertelorism, microtia, etc.). Most

				patients underwent upper airway endoscopy and/or polysomnography. An obstructive AHI <1 episode/h was considered normal, 1-5 episodes/h mild OSAS, 5-24 episodes/h moderate OSAS, and >24 episodes/h severe OSAS. 42 of 59 (71.2%) subjects had one or more sleep studies: 7.1% of patients had mild OSAS; 7.1% had moderate OSAS; and 19% had severe OSAS. 12 of 42 children underwent upper airway endoscopy: in 6 of 12 patients the tongue base was placed against the posterior pharyngeal wall. 69.5% of 59 children were managed with prone positioning only; 10.2% initially were placed in the prone position but subsequently required oxygen administration, nasopharyngeal airway insertion, CPAP or

				mandibular distraction osteogenesis (1 case). 4 of 59 (6.8%) patients required endotracheal intubation in the neonatal period which was followed by tracheostomy and in one case the tracheostomy was followed by mandibular distraction osteogenesis. The remaining 8 patients were managed by intubation (one case), oxygen administration, nasopharyngeal airway insertion or CPAP followed in 4 cases by mandibular distraction osteogenesis. Overall, 8 of 59 (13.6%) subjects were treated with mandibular distraction osteogenesis. 47% of infants were supported by nasogastric or gastrostomy tube feedings. 3 (5%) patients died.

Daniel et al, 2013 [46]	Retrospective, cohort study	IV	39 infants with Robin sequence (1 year old)	10 (25.6%) infants had mild/moderate OSAS (AHI 1-10 episodes/h) but the majority (29 patients or 74.4%) had severe OSAS (AHI >10 episodes/h). More airway interventions were performed in infants with severe OSAS compared to those with mild/moderate OSAS in hospital or at discharge. 30.0% of infants with mild/moderate OSAS were placed on continuous positive airway pressure during admission and 20.0% of infants at discharge. Amongst those with severe OSAS, 82.8% required airway interventions: 17.2% underwent mandibular distraction osteogenesis, and 55.2% required continuous positive airway pressure at discharge. Infants with severe OSAS required tube feeding at discharge more frequently

				than infants with mild/moderate OSAS (89.7% vs 50.0%). Children were at lower weight centiles at discharge compared to birth (-10.2 centiles) and at 12 months of age compared to birth (-14.8 centiles).
Paes et al, 2013 [71]	Systematic review		12 studies including 212 infants (<18 m.o.) with Robin sequence who underwent mandibular distraction osteogenesis.	82% of patients had isolated Robin sequence, 8% had Stickler's syndrome, 2% had Treacher Collins syndrome and 1% had Opitz syndrome. A cleft palate was present in 79% of cases. Upper airway endoscopy and polysomnography in combination with cephalometry and/or 3D CT scans was conducted in most patients. The mean age of initiating mandibular distraction osteogenesis varied from

				8.3 to 9.6 weeks of age. The mean duration of the distraction process varied from 8.5 to 17 days. Tracheostomy was avoided or decannulation was achieved in 82% to 100% of patients.
Rachmiel et al, 2012 [72]	Prospective, cohort study	IV	11 children (4 months to 6 years old) with OSAS and micrognathia who were tracheostomy-dependent	Distraction osteogenesis was used to enlarge the airway and achieve decannulation. Bilateral distraction in the mandibular body was carried out using extraoral distraction devices. Three-dimensional computed tomography reconstruction of the face and neck before and after the intervention demonstrated mandibular elongation of a mean of 30 mm on each side, an increase in mandibular volume by an average of 29.19%, and increase in pharyngeal airway by an average of 70.53%. Two to

				3 months following completion of the intervention, all 11 patients were decannulated with improvement in signs and symptoms of OSAS and no need for supplemental oxygen. Mean follow-up was 2.0 years. The respiratory disturbance index was <2 episodes/h for all patients.
Baciliero et al, 2011 [143]	Retrospective, cohort study	IV	246 infants with isolated Pierre Robin sequence (micrognathia and glossoptosis) aged 3-40 days.	88% of patients had also cleft palate. 118 (48%) subjects were treated with mandibular traction and the remaining patients were managed with non-surgical methods. The average age at the time of mandibular traction was 22 days (range 2–64 days). The intervention was accompanied by improvement in respiratory distress and SpO_2. Decannulation was achieved in 4 infants who

				had a tracheostomy. The average duration of traction treatment was 44 days (range 25–63 days). Nasogastric tube was used for feeding in 90% of cases and was maintained after discontinuation of the traction in the majority of cases. Local infection at the site of the wires was the most frequent complication.
Cheng et al, 2011 [49]	Case series	IV	6 infants who failed treatment with CPAP out of 20 infants with Pierre Robin sequence and respiratory distress.	The follow-up interval was 9 months to 6 years. All infants underwent laryngoscopy and bronchoscopy under general anaesthesia which revealed glossoptosis resulting in near-complete upper airway obstruction while in the prone position. Additional obstructive lesions were found: unilateral choanal atresia, hypoplastic

				epiglottis, laryngomalacia, tracheal stenosis. Preoperative polysomnography demonstrated an average respiratory disturbance index >27 episodes/h. Maximum CO_2 was 56-85 mmHg. Mandibulotomy, insertion of resorbable distractors and glossopexy were performed between 26 days and 11 months of age. Serial polysomnography studies were carried out postoperatively. Average respiratory disturbance index decreased to 7.3 episodes/h and maximum CO_2 to 34-45 mmHg. Weight percentile increased.
Scott et al, 2011 [144]	Retrospective, cohort study	IV	19 infants younger than 3 months (mean age 4.8 weeks; range 5 days–12 weeks) who underwent mandibular distraction	Fourteen infants had isolated Pierre Robin sequence and 5 had syndromic PRS (Stickler syndrome, Marshall-

			osteogenesis due to Pierre Robin sequence and severe upper airway obstruction.	Stickler syndrome, Catel Manzke syndrome, Opitz C syndrome, and arthrogryposis multiplex congenita). The mean duration of follow-up after the procedure was 67 months (range 37-122 months). 90% of patients had an intermediate or good outcome and only one child had a tracheostomy despite the intervention.
Miloro, 2010 [145]	Retrospective, cohort series	IV	35 children (15 female) with upper airway obstruction who underwent mandibular distraction osteogenesis at mean age 3.5 months. At the time of distraction, 28 of 35 patients were younger than 9 months of and 30 patients were younger than 1 month of age.	The patient diagnoses consisted of Pierre Robin sequence (moderate to severe), Stickler syndrome, Opitz syndrome, Down syndrome with OSAS, Goldenhar's syndrome, Treacher Collins syndrome, and mandibular retrognathia not otherwise specified. All patients had frequent apnoeic episodes and repetitive signs and

| | | | | symptoms of upper airway obstruction. Apnoea monitoring demonstrated frequent apnoeic episodes and oxygen desaturation of haemoglobin (70%-80%) in all cases. All patients had obstruction limited to the upper airway related to severe retrognathia and posterior tongue-base displacement that was confirmed with direct laryngoscopy. The mean follow-up period was 9 months (range 4-18 months). Clinically, all patients had improved subjective airway symptoms, before completion of the distraction period, because all patients were extubated or decannulated before the completion of the distraction process. No patient had apneic events post-surgically, and apnoea monitors were discontinued within 1 |

				week by all parents because of a lack of any alarms. Any post-distraction sleep study for OSAS was normal following distraction. All feeding tubes were removed within 3 weeks after distraction, and all patients gained weight appropriate for their age. All children improved clinically prior to completion of the distraction period; all patients were extubated or decannulated. None had apnoeic events postoperatively.
Looby et al, 2009 [74]	Retrospective, cohort study	IV	17 infants with syndromic or non-syndromic micrognathia who underwent mandibular distraction osteogenesis at the average age of 105 days (range 11-310 days)	Surgery was performed if there was no response to conservative measures i.e. prone positioning or nasopharyngeal airway insertion. Failure of conservative treatment was defined as refractory apnoea, inadequate weight

				gain, or lack of parental compliance. Preoperative assessment included 3-dimensional CT of the head and neck, polysomnography, direct or fiberoptic laryngoscopy, modified barium swallow study and esophageal pH testing. These tests were repeated postoperatively. Preoperatively, the mean AHI was 10.6 episodes/h (range 0-43.1 episodes/h), and the mean SpO_2 nadir was 83% (range 66%-98%). Postoperatively, the mean AHI decreased to 2.2 episodes/h (range 0-12.9 episodes/h), and the mean SpO_2 nadir increased to 90% (range, 81%-98%). The mean retroglossal oropharyngeal cross-sectional area increased from 41.53 mm^2 to 127.77 mm^2.

| Meyer et al, 2008 [137] | Retrospective, cohort study | IV | 74 children with Pierre Robin sequence with a median age of 6 months (range 0-11.5 years); 53 with isolated Pierre Robin sequence and 21 with syndrome or neurologic comorbidity. | The main outcomes for efficacy of interventions were CO_2 partial pressure in capillary blood and oxygen saturation of haemoglobin. 49% of patients required no airway interventions or responded to prone positioning; 19% of children were managed with a nasopharyngeal airway; 32% of patients required mandibular distraction osteogenesis, tracheostomy or tracheostomy followed by mandibular distraction osteogenesis. 75% of patients who required surgical treatment did not respond to a trial of nasopharyngeal airway insertion. 51% of children were fed by nasogastric tube, 19% by gastrostomy tube and 30% had initially a nasogastric tube which was replaced by a gastrostomy tube. |

| Ow et al, 2008 [146] | Meta-analysis | | 178 articles including 1185 patients who underwent mandibular distraction osteogenesis (539 had unilateral procedure; 646 had bilateral procedure) | Patients who underwent unilateral procedure were most commonly aged 6-10 years and had hemifacial or craniofacial macrosomia. Subjects who underwent bilateral mandibular osteogenesis were <2 year old in 21.4% of cases and 2-5 year old in 19.3% of cases with most common diagnoses: Pierre Robin sequence, class II mandibular hypoplasia, Treacher Collins syndrome, obstructive sleep apnoea and temporomandibular joint ankyloses. Children with Pierre Robin sequence, Treacher Collins syndrome or other congenital micrognathia had respiratory distress and/or obstructive sleep apnoea and they underwent bilateral distraction osteogenesis. |

				Tracheostomy was prevented in 91.3% of neonates or infants; 78.4% of patients with tracheostomy were decannulated; and obstructive sleep apnoea resolved or improved in 97% of pediatric patients.
Schaefer et al, 2004 [50]	Retrospective, cohort study	IV	21 patients with isolated Pierre Robin sequence treated by one surgeon over a 9-year period; 18 of 21 infants presented during the first week of life; 3 other infants were 12-33 months old.	Patients were followed for a median period of 33 months (range 9-70 months). Airway patency was achieved with prone positioning for 10 (47.6%) patients, with tongue-lip adhesion for 7 of 10 (47.6%) patients who underwent the procedure, with tracheostomy for 2 (9.5%) patients, and with mandibular distraction osteogenesis for 3 (14.3%) patients. There was significant change in the maxillary-mandibular discrepancy during the first 1 year of life (P

				<0.0001). Oromotor studies performed ≥3 months after reversal of tongue-lip adhesion reversal (n = 9) demonstrated no deficits in tongue function, relative to other children with cleft lips/palates.
Morovic et al, 2000 [147]	Retrospective, cohort study	IV	7 patients (aged 1-18 months) with mandibular hypoplasia and critical OSAS (AHI>20 episodes/h and oxygen saturation of haemoglobin <80%) who underwent mandibular distraction osteogenesis.	Two patients had already a tracheostomy. Mandibular lengthening (16-25 mm on the left side; 10-22 mm on the right side) was achieved in 21-25 days. Improvement of airway obstruction was demonstrated by polysomnography and cephalometry.

5.7. What are the indications and risks of tracheostomy for OSAS in young children?

a+b+c. *Efficacy and complications of tracheostomy*

Author, year	Type of Study	Class	Subjects	Methods and findings
Driessen et al, 2013 [42]	Prospective, cohort study	III	97 children with syndromic craniosynostosis	Patients were classified in those with: Apert, Crouzon and Pfeiffer syndromes which are accompanied by midface hypoplasia (subgroup 1); Muenke and Saethre-Chotzen syndrome and complex craniosynostosis (subgroup 2). A sleep study was performed at age 1, 2, 3, 4, 5 and 6 years old and once every 3 years after the age of 3 years (at 9, 12, 15 and 18 years old). If there were abnormal findings the sleep study was repeated within 3–6 months. OSAS was defined as obstructive AHI ≥ 1 episode/h; OSAS was considered as: mild if obstructive AHI <5 episodes/h; moderate if AHI 5–24 episodes/h; and severe if AHI ≥25 episodes/h. OSAS prevalence was 68%; 25 (26%) patients had moderate-to-severe OSAS and 64% of

				them had midface hypoplasia. 23 of 97 (23.7%) children were treated for OSAS due to snoring, difficulty breathing, restless sleep and/or nocturnal sweating but only 5 (21.7%) had moderate-to-severe disease. The majority of patients underwent cranial vault remodeling before the age of 1 year. Treatment for OSAS was offered at a median age of 4.5 years (range 4 months-18 years old). Adenotonsillectomy was the most frequent intervention (n=20) followed by transverse widening of the hypoplastic maxilla with a hyrax expander (n=1), midface advancement (n=6), tracheostomy (n=3) or ventilation (n=2). A longitudinal analysis was carried out for 80 untreated patients. Children with midface hypoplasia had higher obstructive AHI compared to children without

				midface hypoplasia. Obstructive AHI decreased significantly over the first 3 years of life.
Leonardis et al, 2013 [89]	Retrospective, cohort study	IV	126 neonates and infants (aged 0-12 months) diagnosed with OSAS	Polysomnography was performed and OSAS was diagnosed if AHI ≥1.5 episodes/h. Mild OSAS was defined as AHI 1.5-4.9; moderate OSAS as AHI 5-14.9; and severe OSAS as AHI ≥15 episodes/h. Response to treatment interventions was scored by family members or caregivers as: -1 for worsening, 0 for no change, 1 for mild improvement, 2 for moderate improvement, and 3 for significant improvement or resolution. The percentage change in the AHI between pre-intervention and post-intervention was also calculated. 40 patients had mild OSAS; 44 had moderate OSAS; and 42 had severe

				OSAS. 68.3% of subjects had gastroesophageal reflux; 36.5% had a congenital syndrome or craniofacial malformation [Down syndrome (7.9%); cleft palate (7.1%); Pierre Robin sequence (4.8%); achondroplasia (4.8%); Prader-Willi syndrome (1.6%)]; other diagnoses were: laryngomalacia (28.6%); hypotonia (13.5%); and Chiari malformation (5.6%). The frequency of each treatment intervention was: anti-reflux medications (69.8%), observation (26.2%), supplemental oxygen (24.6%), adenoidectomy (23.8%), other surgical treatment (19.8%), CPAP/NPPV) (14.3%), supraglottoplasty (8.7%), adenotonsillectomy (7.1%), tracheostomy (5.6%), and other nonsurgical (5.6%). Other nonsurgical interventions were caffeine administration

| | | | | and blood transfusion in cases of prematurity. Other surgical interventions included: neurosurgical decompression (ventriculoperitoneal shunt placement, meningomyelocele closure, Chiari decompression and intraventricular cyst fenestration); mandibular distraction osteogenesis; palatoplasty; tongue base reduction; nasal stent; aortopexy. Pre- and post-intervention polysomnography was performed in 41.3% of subjects. Observation was the most subjectively effective intervention (mean value 2.8 on caregivers' scale). Tracheostomy had a mean subjective score of 2.7. For patients who had both pre-intervention and post-intervention sleep study, CPAP/NPPV had the highest mean % reduction in the AHI (-67.2%), followed by |

				tracheostomy (-67.0%), observation (-65.6%), and supraglottoplasty (-65.3%).
van Lieshout et al, 2014 [45]	Retrospective, cohort study	IV	59 infants with Robin sequence born between 2000-2010 (49% females; age < 1 year)	61% of patients had isolated Robin sequence; 14% had syndromic Robin sequence (Treacher Collins syndrome, Stickler syndrome, Nager syndrome, Miller syndrome, Trisomy 19, chromosome 11 duplication); 25% had associated abnormalities without a diagnosed syndrome (hypertelorism, microtia, etc.). Most patients underwent upper airway endoscopy and/or polysomnography. An obstructive AHI <1 episode/h was considered normal, 1-5 episodes/h as mild OSAS, 5-24 episodes/h as moderate OSAS, and >24 episodes/h as severe OSAS. 42 of 59 (71.2%) subjects had one or more sleep studies: 7.1% of patients had mild OSAS;

				7.1% had moderate OSAS; and 19% had severe OSAS. 12 of 42 children underwent upper airway endoscopy: in 6 of 12 patients the tongue base was placed against the posterior pharyngeal wall. 69.5% of 59 children were managed with prone positioning only; 10.2% initially were placed in the prone position but subsequently required oxygen administration, nasopharyngeal airway insertion, CPAP or mandibular distraction osteogenesis (1 case). 4 of 59 (6.8%) patients required endotracheal intubation in the neonatal period which was followed by tracheostomy and in one case the tracheostomy was followed by mandibular distraction osteogenesis. The remaining 8 patients were managed by intubation (one case), oxygen administration, nasopharyngeal airway

				insertion or CPAP followed in 4 cases by mandibular distraction osteogenesis. 47% of infants were supported by nasogastric or gastrostomy tube feedings. 3 (5%) patients died.
Robison et al, 2013 [99]	Retrospective, cohort study	III	295 infants diagnosed with OSAS (AHI ≥1.5 episodes/h) with OSAS at the age of 3 to 24 montsh and with follow-up ≥6 months later.	OSAS was graded as mild (AHI 1.5–4.9 episodes/h), moderate (AHI 5.0–14.9 episodes/h), or severe (AHI ≥15 episodes/h). The most common interventions with average age at the time of intervention were: adenotonsillectomy, 115 patients (31.8%, 22.3 months); adenoidectomy, 82 patients (22.5%, 17.7 months); observation, 76 patients (20.9%, 12.8 months); supplemental oxygen, 27 patients (7.4%, 11.7 months); CPAP/bilevel positive airway pressure (BPAP), 18 patients (4.9%, 15.6 months); tonsillectomy, 16 patients (4.4%, 25.7

				months); and tracheostomy, six patients (1.7%, 15.3 months). In patients aged 3–5 months, 89.3% of interventions were nonsurgical and 10.7% were surgical. In patients older than 24 months, 17.5% of interventions were nonsurgical and 82.5% were surgical. Subjective improvement following intervention was highest after adenotonsillectomy. The intervention with the greatest reduction in AHI was tracheostomy, followed by CPAP/BPAP.
Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 2; moderate if the McGill oximetry score was 3; and severe if the McGill oximetry score was 4. The presence of obstructive events and increased work of breathing

				was used to re-classify UAO severity if necessary. When UAO was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. The average duration of hospitalisation after nasopharyngeal airway insertion was 10 days (range 6–28 days). For infants discharged with an artificial airway, the immediate post-insertion sleep study

				revealed no UAO in 7.9% of cases, mild UAO in 61.9% and moderate UAO in 30.2%. The average duration of nasopharyngeal airway use was 8 months (3 weeks to 27 months); 88.9% of infants had the nasopharyngeal airway removed before the age of 12 months. Of patients who required tracheostomy, 64.2% were decannulated at a median age of 3 years (range 2-5 years), whereas the remaining subjects continued to have tracheostomy or underwent mandibular distraction osteogenesis surgery. 82 of 104 (78.8%) infants required feeding with a nasogastric tube for a few weeks to months. No fatalities related to upper airway obstruction were reported.
Ahmad et al, 2012 [132]	Retrospective, cohort study	IV	12 children younger than 30 months with severe	One child had Apert syndrome, 6 had Crouzon

			syndromic craniofacial dysostosis who underwent monobloc frontofacial advancement with a rigid external distractor frame (mean age, 18 months; range 4-30 months).	syndrome and 5 had Pfeiffer syndrome. All participants had moderate-to-severe upper airway obstructions as demonstrated by polysomnography. 9 patients had tracheostomy prior to craniofacial surgery and 3 had tracheostomy to secure a patent airway for the operation; 8 had raised intracranial pressure. All patients underwent frontofacial monobloc surgery by distraction osteogenesis using a rigid, external distractor frame. Mean follow-up postoperatively was 25 months (range 6 months to 5 years). 7 patients were decannulated. Raised intracranial pressure resolved in all cases. Two children had cerebrospinal fluid leak (meningitis in one case). Three cases of pin-site infections required treatment with topical and/or systemic antibiotics. Two children had

				the rigid external distraction frame repositioned and one patient died 9 months later following a tracheal reconstruction procedure.
Meyer et al, 2008 [137]	Retrospective, cohort study	IV	74 children with Pierre Robin sequence with a median age of 6 months (range 0-11.5 years); 53 with isolated Pierre Robin sequence and 21 with syndrome or neurologic comorbidity.	The main outcomes for efficacy of interventions were CO_2 partial pressure in capillary blood and oxygen saturation of hemoglobin. 49% of patients required no airway interventions or responded to prone positioning; 19% of children were managed with a nasopharyngeal airway; 32% of patients required mandibular distraction osteogenesis, tracheostomy or tracheostomy followed by mandibular distraction osteogenesis. 75% of patients who required surgical treatment did not respond to a trial of nasopharyngeal airway insertion. 51% of children were fed by nasogastric tube, 19% by

				gastrostomy tube and 30% had initially a nasogastric tube which was replaced by a gastrostomy tube.
Schaefer et al, 2004 [50]	Retrospective, cohort study	IV	21 patients with isolated Pierre Robin sequence treated by one surgeon over a 9-year period; 18 of 21 infants presented during the first week of life; 3 other infants were 12-33 months old	Patients were followed for a median period of 33 months (range 9-70 months). Airway patency was achieved with prone positioning for 10 (47.6%) patients, with tongue-lip adhesion for 7 of 10(47.6%) patients who underwent the procedure, with tracheostomy for 2 (9.5%) patients, and with mandibular distraction osteogenesis for 3(14.3%) patients. There was significant change in the maxillary-mandibular discrepancy during the first 1 year of life (P <0.0001). Oromotor studies performed ≥3 months after reversal of tongue-lip adhesion reversal (n = 9) demonstrated no deficits in tongue function, relative to other children with

				cleft lips/palates.
Kremer et al, 2002 [148]	Review		49 publications including children who underwent tracheostomy. The proportion of children younger than 1 year was 44% to 63%.	23% of children had congenital malformations; 58% of children had history of prematurity; 23% had acquired subglottic stenosis; 23% had neuromuscular disease. The most frequent early complication was development of interstitial air (emphysema, pneumomediastinum, pneumothorax). Bleeding occurred in up to 7% of children older than 12 months and in up to 5% of newborns and premature infants. Accidental decannulation and cannula obstruction are life-threatening complications.
Li et al, 2002 [107]	Retrospective, cohort study	IV	110 children with Pierre Robin sequence (64 with cleft palate) over 10 years; 85% of patients ≤3 months old	Prone posturing was effective in the treatment of mild airway obstruction in 82 (74.5%) patients with noisy breathing. 28 (25.5%) infants were intubated for severely

				increased work of breathing (maximum duration 3 weeks); 7 (6.4% of total cases) had a tongue-to-lip adhesion and 3 of them had relief of upper airway obstruction, whereas in the other 4 rupture of the wound occurred and they underwent tracheostomy; 2 additional patients had tracheostomy without any other intervention; patients with tracheostomy were decannulated successfully. One of 2 patients who had insertion of a nasopharyngeal tube was relieved temporarily. 46 (41.8%) patients required nasogastric tube feeding; none of the patients required gastrostomy.
Marques et al, 2001 [109]	Prospective, cohort study	IV	62 infants with Pierre Robin sequence aged <6 months old; 53.2% of infants had isolated Pierre Robin sequence	All patients underwent nasopharyngoscopy. Upper airway obstruction was classified in 4 types according to Sher et al

				(1992). 75.8% of infants (90.9% of those with isolated Pierre Robin sequence) had type 1 obstruction; 12.9% type 2 obstruction; 6.5% type 3 obstruction; and 4.8% type 4 obstruction. Response to treatment was defined as good pulmonary ventilation, reduced work of breathing and apnea, oxygen saturation of haemoglobin >90% and tolerance of oral feeding. Prone positioning or nasopharyngeal airway insertion were adequate interventions in 76.6% and 50% of patients with type 1 or type 2 obstruction, respectively; 14.5% of infants with type 1 obstruction underwent glossopexy. The remaining infants and 100% of those with type 3 or type 4 obstruction required tracheostomy (overall frequency of tracheostomy 20.9%). Overall fatality rate was 11.3%.

Perkins et al, 1997 [149]	Retrospective, cohort study	IV	109 patients with craniofacial anomalies affecting the midface and/or the mandible	Patients' diagnoses included: Pierre Robin sequence, Apert syndrome, Treacher Collins syndrome, Saethre-Chotzen, CHARGE association, Nager syndrome, Stickler syndrome, Goldenhar syndrome, and Pfeiffer syndrome. The type of airway intervention, duration of intervention, and associated physical and medical conditions were reviewed. Sixty-five of these patients required airway intervention, most commonly in the first month of life, ranging from positioning to tracheotomy. Nineteen patients required a tracheostomy.
Sher et al, 1992 [51]	Retrospective, cohort study	IV	53 infants with Robin sequence aged 1 day to 9 months.	All infants underwent nasopharyngoscopy and type of obstruction was classified according to Sher et al, 1986: Type I obstruction in 58.5% of infants; type II in 20.8%;

				type III in 9.4%; and type IV in 9.4% of infants. 48 (90.6%) patients responded well to insertion of nasopharyngeal tube. 24 infants (all with type I obstruction) underwent glossopexy. 7 infants with pharyngeal obstruction types II-IV who did not respond to insertion of nasopharyngeal tube required tracheostomy.

5.8. What is the management of OSAS in young children with complex conditions?				
a. *Achondroplasia*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Afsharpaiman et al, 2011 [102]	Retrospective, cohort study	IV	46 children aged 3 months to 14 years over a 15-year period; 25 of 46 subjects had age ≤2 years.	25 (54.3%) patients had OSAS. Mean AHI was 11.2 ± 7.3 episodes/h and minimum SpO_2 was 85.8 ± 5.4% in children ≤2 years old. Children with OSAS tended to be younger than those without OSAS.

				Participants aged ≤2 years had more frequently OSAS (16 of 25 or 64.0%; P=0.01) than older patients, that was significantly more severe (p=0.004) and with deeper oxyhaemoglobin desaturations (p=0.004). Amongst patients ≤2 years old, adenotonsillectomy was the only treatment intervention for 33.0% of children >2 years old compared to 24.0% of those ≤2 years old. CPAP was applied in 9.8% of patients >2 years old vs. 28% of those ≤2 years old. Amongst patients ≤2 years old, two children were treated with CPAP for severe OSAS that persisted or deteriorated after adenotonsillectomy and five children had only CPAP. Treatment interventions were accompanied by improvement in

Tasker et al, 1998 [150]	Prospective, cohort study	IV	17 infants (3 girls) with achondroplasia and respiratory symptoms before 1 year of age	polysomnography indices. Group 1 infants (n = 6) had only OSAS, large adenotonsillar tissue relative to the degree of midfacial hypoplasia and improvement following adenotonsillectomy. Group 2 (n = 6) had persistent OSAS despite adenotonsillectomy and hydrocephalus with a small foramen magnum. Group 3 (n = 5) had OSAS, central apnoeas and cor pulmonale and 3 of them died due to progressive cardiorespiratory failure. All children had a small foramen magnum and moderately-to-severe gastroesophageal reflux.
b. *Chiari malformation*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Amin et al, 2015 [151]	Retrospective, cohort study	IV	68 children with Chiari I malformation who	19% of patients had undergone adenoidectomy

				underwent polysomnography at the age of 7.33 ± 4.01 years. Eight children were excluded because they were technology-dependent (supplemental oxygen, CPAP, BPAP, or tracheostomy and mechanical ventilation).	or tonsillectomy. The prevalence of SDB (AHI ≥2 episodes/h and/or hypoventilation) was 49%. OSAS was the predominant type of SDB (24% of patients had obstructive AHI ≥2 episodes/h). 18% of children had central apnea index ≥5 episodes/h and 9% of children had nocturnal hypoventilation. Tonsillar herniation was significantly correlated with obstructive AHI (r=0.24; P=0.036).
Khatwa et al, 2013 [59]	Retrospective, cohort study	IV	22 children with Chiari malformation type I (11 males median age 10 years, range 1-18 years)	3 children had central sleep apnoea, 5 had OSAS and one child had both obstructive and central sleep apnoeas. Children with SDB had excessive crowding of the brainstem structures at the foramen magnum and greater length of herniation relative to children

				without SDB. Patients with central sleep apnoeas underwent surgical decompression, with improvement in polysomnography.
c. *Down syndrome*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Cockerill et al, 2016 [152]	Retrospective, cohort study	IV	18 infants with Down syndrome who underwent supraglottoplasty for laryngomalacia at the average age of 7.7 months (0.6-25 months).	Indications for surgery included: feeding difficulties (n=9); noisy breathing, respiratory distress or both (n=16); and sleep-related symptoms (n=7). Most patients (89%) were extubated successfully on postoperative day 1. One patient required CPAP postoperatively and a second patient developed aspiration pneumonia). 50% of infants had a mean improvement of 17.6 percentile points in weight. Feedback was available from 88% of parents with 100%

				reporting improvement in respiratory symptoms and 93% reporting improved feeding. Preoperative and postoperative polysomnograms were available for 4 patients. The median reduction in AHI postoperatively was 6.5 episodes/h (range 5-58 episodes/h). All 4 patients had AHI <5 episodes/h postoperatively, but in one case a revision supraglottoplasty was required to achieve this result. Additional interventions were required subsequently: 8 (44%) patients had adenoidectomy or adenotonsillectomy; 2 patients underwent tracheostomy; 2 patients needed a gastrostomy tube; and 2 required revision supraglottoplasty.
Rosen et al, 2010 [153]	Retrospective, cohort	IV	29 children with Down	16 of 29 infants studied

| | | | syndrome and suspected OSAS aged <2 years | had OSAS (obstructive AHI >1 episode/h); 6 were treated with CPAP and 3 of them had no OSAS on polysomnography 5-10 months later. Moreover, one patient was treated with supplemental oxygen at night, 2 underwent adenoidectomy and 4 underwent adenotonsillectomy. |
| study | | | | |

d. *Mucopolysaccharidoses*

Author, year	Type of Study	Class	Subjects	Methods and findings
Pal et al, 2015 [65]	Retrospective, cohort study	IV	61 children with type I mucopolysaccharidosis (44 Hurler phenotype, 17 attenuated cases) who underwent nocturnal oximetry between 6 months pre- to 16 years post-treatment (median follow-up 22 months).	A total of 150 sleep oximetry studies were analysed. SDB was defined as ODI 4% > 5 episodes/h and median SpO_2 <95%. Moderate SDB was diagnosed if ODI4% was 5–10 episodes/h and severe SDB as ODI4% >10 episodes/h. The incidence of SDB was 68% and 16% of participants required therapeutic intervention

				for airway obstruction. Greater frequency of SDB progression and requirement for treatment intervention were demonstrated amongst patients under enzyme replacement therapy as compared to those who underwent haematopoietic stem cell transplantation.

e. *Prader-Willi syndrome*

Author, year	Type of Study	Class	Subjects	Methods and findings
Khayat et al, 2017 [154]	Retrospective, cohort study	IV	28 (12 male) infants with Prader-Willi syndrome who had baseline polysomnography at median age of 0.9 years (interquartile 0.5 to 1.1 years).	The median central apnoea index at baseline was 6.6 episodes/h (interquartile range 2.6 to 12.1 episodes/h). 15/28 (53%) infants had central apnoea index ≥5 episodes/h. Median age at follow-up was 2.1 years (interquartile range 1.5 to 2.6 years). The median central apnoea index improved from 6.6 to 2.3 episodes/h (P<0.0001). 4 of 15 infants had

				persistent central sleep apnoea at the time of the follow-up polysomnogram. 3 of 18 infants with Prader-Willi syndrome were diagnosed with mild-to-moderate OSAS which improved at follow-up studies, whereas 2 patients with no evidence of OSAS at baseline were diagnosed with severe OSAS during follow-up requiring adenotonsillectomy. The overall median obstructive AHI was similar between baseline and follow-up studies (0.6 and 0.8 episodes/h, respectively, P=0.91).
Urquhart et al, 2013 [104]	Retrospective, cohort study	IV	10 infants (8 female) with Prader-Willi syndrome aged 0.06-1.79 (median 0.68) years.	All patients underwent full polysomnography, and supplemental oxygen was administered to those with frequent desaturations accompanying central events during sleep. They

				were followed with regular split-night studies (periods in room air and with supplemental oxygen). Thirty split-night studies were completed. In room air, children with Prader-Willi syndrome had a median central apnoea index of 4.7 (interquartile range: 1.9, 10.6) episodes/h, with accompanying falls in oxygen saturation (SpO_2). Oxygen supplementation was related to significant reductions in central apnoea index to 2.5 episodes/h (P=0.002) and improved SpO_2. No change in the number of obstructive events was noted. Central events were more frequent in REM/active sleep.
Meyer et al, 2012 [155]	Retrospective, cohort study	IV	13 children with Prader-Willi syndrome who underwent	Median age at initiation of growth hormone treatment was 8.5 months (range: 2

			adenotonsillectomy (median age 3 years; range: 2 months to 6 years) and polysomnography pre- and postoperatively	months to 6 years). 9 of 13 patients (69%) had mild to moderate OSAS or obstructive hypoventilation; in 8 of these 9 children, SDB resolved postoperatively. 4 (31%) children had severe OSAS prior to surgery (31%). Breathing normalized in 2 of these after surgery, but 2 had residual obstructive and central apnoeas.

Online Supplementary Table S6

Topic 6: Follow-up, recognition and management of persistent OSAS in young children

Question 6.1. How soon after each treatment is the young child with OSAS usually re-evaluated and what outcomes are monitored?				
a. *Monitoring after adenotonsillectomy*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Nath et al, 2013 [112]	Retrospective, cohort study	IV	283 patients (mean age, 22 ± 7 months) who underwent adenotonsillectomy had preoperative	In the group with both preoperative and postoperative polysomnography, there were statistically

				polysomnography and 70 of them had also postoperative polysomnography.	significant improvements in AHI (from 34.8 ± 40.7 episodes/h to 5.7 ± 13.8 episodes/h; $P < 0.001$), baseline SpO_2 (from $96.6\% \pm 2.1\%$ to $97.2\% \pm 1.4\%$; $P = 0.05$), minimum SpO_2 (from $77.2\% \pm 11.4\%$ to $89.9\% \pm 6.8\%$; $P < 0.001$), and sleep efficiency (from $84.7\% \pm 14.9\%$ to $88.7\% \pm 9.1\%$; $P = 0.02$) after adenotonsillectomy. When AHI >5 episodes/h was used to define OSAS, 21% of the patients had residual disease. The most consistent predictor of residual OSAS postoperatively was the severity of preoperative disease ($P = 0.02$).
Greenfeld et al, 2003 [15]	Prospective, cohort study		IV	29 consecutive infants <18 months of age who underwent polysomnography and were diagnosed with	A pediatric sleep questionnaire was completed by parents of all infants. Information regarding recurrence of

			OSAS due to adenotonsillar hypertrophy	OSAS symptoms post-treatment was collected. Two infants underwent adenoidectomy only and the rest of them had adenotonsillectomy. The mean age at adenotonsillectomy was 12.3 ± 3.9 months and the mean duration of OSAS symptoms prior to adenotonsillectomy was 6.2 ± 3.0 months. 24% of the infants had history of premature birth. Snoring was reported in all infants. Other symptoms included: sleep apnoea (72%), frequent movements during sleep (69%), mouth breathing (62%) and recurrent awakenings (38%). Furthermore, mean body weight decreased from the $67^{th} \pm 25^{th}$ percentile to the $42^{nd} \pm 32^{nd}$ percentile (P<0.001). 14/29 (48%) of the infants dropped two or more major percentiles prior to

				surgery. Following surgery, significant weight gain increase to the $59^{th} \pm 31^{st}$ percentile was demonstrated (P<0.0001). 5 of 29 (17%) infants were considered by their parents as having a developmental delay preoperatively, which resolved in 3/5 (60%) postoperatively. Clinical symptoms resolved or improved significantly after surgery. Recurrence of symptoms was documented in 6 of 23 (26%) of infants as soon as 6 months post-adenotonsillectomy and repeat adenoidectomy was required.
b. *Monitoring during CPAP treatment*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Amaddeo et al, 2016 [119]	Retrospective, cohort study	IV	44 neonates with Pierre Robin sequence over a period of 1 year	i) Severe upper airway obstruction: inability to breathe spontaneously and maintain normoxia and normocapnia without

				invasive or noninvasive positive pressure ventilation; ii) moderate upper airway obstruction: AHI >10 episodes/h and or desaturation index >15 episodes/h and/or SpO_2 nadir <90% and/or maximum end-tidal carbon dioxide level >50 mHg (daytime nap polygraphy). In the severe upper airway obstruction group, CPAP was used for 24 h per day initially and over the next 1-2 weeks was progressively applied only during sleep periods. In the moderate upper airway obstruction group, CPAP was used only during sleep periods. The interface used was a nasal mask and the starting pressure was 6 cmH_2O which was increased rapidly to the required level. Tracheostomy was performed if patient was dependent on mechanical

				ventilation by endotracheal tube or CPAP treatment was not successful. 24 of 44 patients did not have upper airway obstruction. 9 of 44 patients had severe upper airway obstruction; 5 of them responded to CPAP and 4 required tracheostomy. 11 of 44 patients underwent polygraphy and 7 of them had a normal study. The rmaining 4 patients had AHI 19-42 episodes/h, desaturation index 18-137 episodes/h, SpO_2 nadir 78-90% and maximum end-tidal carbon dioxide 41-55 mmHg. All 9 patients with moderate-to-severe upper airway obstruction tolerated nasal CPAP and were discharged home after a median of 30 days (range 20-40 days). The required airway pressure was 6-8 cmH_2O. 5 of 9 infants were weaned off

				CPAP after 1-5.5 months and 4 of 5 were still on CPAP during the study (4 months).
Massa et al, 2002 [125]	Retrospective, cohort study	IV	66 children aged 0-19 years with OSAS who were considered for nCPAP treatment. 18 (27%) patients were younger than 1 year; 28 (42%) were aged 1 to 5 years; 12 (18.2%) were 6 to 12 years old and 8 (12.1%) were 13-19 years old.	Moderate-to-severe OSAS was defined as: i) obstructive apnoea index $\geq$5 episodes/h; and/or desaturation ($\geq$4% lasting >10 s) index $\geq$4 episodes/h and SpO_2 nadir <90%. 24 of 66 children had craniosynostosis, 8 had mucopolysaccharidosis, 6 had neuromuscular disease, 2 had Down syndrome and 3 had laryngotracheomalacia or bronchomalacia. nCPAP was started at 4 cmH_2O and titrated up by 2 cmH_2O until OSAS and oxyhaemoglobin desaturations resolved. 42 of 66 (63.6%) children tolerated nCPAP treatment. Follow-up clinical evaluations and

				sleep studies were performed at 1, 6 and 12 months to assess the efficacy of nCPAP, re-adjust airway pressure and the mask size. Patients used nCPAP for a period of 2 months to 6.5 years. Mean airway pressure was 8.5 cmH$_2$O (range 4-16 cmH$_2$O). Minor complications related to mask fit (eye or skin irritation) or nasal dryness were noted.
McNamara et al, 1999 [127]	Retrospective, cohort study	IV	24 infants (9 female) with OSAS aged 1-51 weeks	Patients included in the study had family history of SIDS, apparent life-threatening event, micrognathia, choanal atresia, laryngomalacia, Beckwith-Wiedemann syndrome, Smith-Lemli-Opitz syndrome or Moebius syndrome. Nasal CPAP treatment was initiated if the obstructive-mixed apnoea index was

				greater than 5 episodes/h. Initial pressure required was 3.7 to 6 cmH$_2$O. Both the obstructive apnoea index and desaturation index decreased significantly. The mean obstructive apnoea index was 43.6 ± 8.3 episodes/h in REM sleep and 14.6 ± 3.9 episodes/h in NREM sleep and decreased to 0.4 ± 0.1 episodes/h and 0.1 ± 0.1 episodes/h, respectively with CPAP (P <0.05). Clinical evaluation and polysomnography were repeated every 2-4 months during the first year of life and every 6 months thereafter. 18 infants tolerated CPAP and were treated for 1month to 4.3 years. 5 infants, all with micrognathia or choanal atresia used CPAP for over 2 years with airway pressures between 6.5 and 10 cmH$_2$O. When nasal

				CPAP was initiated in these 5 infants, an average pressure of 4.6 ± 0.2 cm cmH$_2$O was required to prevent obstructive events; after 2 to 4.3 years the average pressure was increased to 7.7 ± 0.7 cmH$_2$O (P <0.05). In 13 infants (mostly those with history of apparent life-threatening events or family history of SIDS) OSAS resolved.
Guilleminault et al, 1995 [128]	Retrospective, cohort study	IV	74 infants (39 girls) with SDB and narrow upper airway who were treated with nasal CPAP (mean age 24 ± 9 weeks).	Presenting symptoms were: apparent life-threatening event (n=17; 23%); failure to thrive (n=8; 11%); abnormal breathing pattern (n=49; 66%). 38 infants had syndromic conditions: Down syndrome (n=7); Pierre Robin (n=7); cleft palate (n=2); Treacher Collins (n=2); Hunter syndrome (n=1); achondroplasia (n=3);

				cerebral palsy (n=7); epilepsy with monoplegia (n=2); hemiplegia (n=2); unclassified muscle disorder (n=1); hydrocephalus with shunt (n=1). 57 (77%) had apparent or subtle craniofacial abnormalities (e.g. high-arched hard palate or small chin). 41.9% of patients had an AHI >25 episodes/h; 37.8% had an AHI 1-25 episodes/h; 9.5% had an AHI 5-10 episodes/h; and 10.8% had an AHI <5 episodes/h. 72 of 74 infants were treated successfully with CPAP. Mean follow-up was 35 ±21 months. 28 (38.9%) patients eventually discontinued CPAP and 37 (51.4%) were still using CPAP at the time of the study.
d. *Monitoring improvement after supraglottoplasty*				

Author, year	Type of Study	Class	Subjects	Methods and findings
Powitzky et al, 2011 [32]	Retrospective, cohort study	III	20 infants (<1 y. o.) who underwent supraglottoplasty for severe laryngomalacia (failure to thrive or signs of severe respiratory distress, such as cyanotic spells, severe intercostal retractions, or prolonged apnoeas with significant desaturations while awake) or moderate laryngomalacia (stridor and associated retractions or dysphagia).	Patients underwent polysomnography pre- and post-supraglottoplasty. Outcome measures included changes in stridor, SDB, swallowing, and polysomnography parameters before and after surgery. Statistically significant improvements were demonstrated 1.1-5.8 months postoperatively in median AHI (-6.4 episodes/h; P=0.02).
e. *Monitoring of patients with Pierre Robin sequence and nasopharyngeal airway or orthodontic appliance*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Buchenau et al, 2017 [135]	Retrospective, cohort study	IV	122 infants with isolated and 85 infants with syndromic Robin sequence aged 4-42 days on admission	Median mixed obstructive apnoea index at baseline was 8.8 (range 2.1–19.7) episodes/h. 55 (45%) infants had severe OSAS (mixed obstructive apnoea index >10 episodes/h). Mixed obstructive apnoea index was significantly decreased at discharge and

				3 months later. None of them required mechanical ventilation or tracheostomy. A nasogastric feeding tube was necessary in 66% of cases on admission and in 8% of cases at discharge. Weight improved from a median z-score −0.7 (−1.39 to −0.24) at admission to −0.5 (−0.90 to +0.02) at 3 months after discharge (P=0.021). The most frequent side effect was tender spots on the hard or soft palate.
Abel et al, 2012 [47]	Retrospective, cohort study	IV	104 patients with Pierre Robin sequence (micrognathia, glossoptosis, cleft palate) who had a sleep study between 2000 and 2010 (age 1 day-12 months); 64/104 were younger than 4 weeks old when referred for evaluation.	Upper airway obstruction (UAO) was considered: mild if oximetry was scored as McGill oximetry score 1; moderate if the McGill oximetry score was 2; and severe if the McGill oximetry score was 3. The presence of obstructive events and increased work of

				breathing was used to re-classify UAO severity if necessary. When UAO was mild, the child had a trial of prone positioning, feeding and management of reflux. If UAO was moderate-to-severe, a nasopharyngeal airway was inserted. A follow-up sleep study was performed at baseline and was repeated every 2 months. UAO was mild in 25.9% of cases and was managed with prone positioning. The remaining patients had moderate or severe UAO and were treated with insertion of nasopharyngeal airway with satisfactory results in 81.8% of them and need for tracheostomy in only 13.4% of cases. For infants discharged with an artificial airway, the immediate post-insertion sleep study

				revealed no UAO in 7.9% of cases, mild UAO in 61.9% and moderate UAO in 30.2%. Sleep studies for monitoring were carried out every 2 months. The average duration of nasopharyngeal airway placement was 8 months (3 weeks to 27 months); 88.9% of infants had the nasopharyngeal airway removed before the age of 12 months. After removal of the artificial airway, follow-up sleep studies were performed every 2 months and most patients underwent at least 5-6 sleep studies. Of patients who required tracheostomy, 64.2% were decannulated at a median age of 3 years (range 2-5 years), whereas the remaining subjects continued to have tracheostomy or underwent mandibular distraction osteogenesis

				surgery.

f. *Monitoring of patients with Pierre Robin sequence who undergo mandibular distraction osteogenesis*				
Author, year	**Type of Study**	**Class**	**Subjects**	**Methods and findings**
Cheng et al, 2011 [49]	Case series	IV	6 infants who failed treatment with CPAP out of 20 infants with Pierre Robin sequence and respiratory distress.	The follow-up interval was 9 months to 6 years. All infants underwent laryngoscopy and bronchoscopy under general anaesthesia which revealed glossoptosis resulting in near-complete upper airway obstruction while in the prone position. Additional obstructive lesions were found: unilateral choanal atresia, hypoplastic epiglottis, laryngomalacia, tracheal stenosis. Preoperative polysomnography demonstrated an average respiratory disturbance index >27 episodes/h. Maximum CO_2 was 56-85 mmHg. Mandibulotomy, insertion of resorbable

				distractors and glossopexy were performed between 26 days and 11 months of age. Serial polysomnography studies were carried out postoperatively. Average respiratory disturbance index decreased to 7.3 episodes/h and maximum CO_2 to 34-45 mmHg. Weight percentile increased.

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