REVIEW ARTICLES

Objective measurements for upper airway obstruction in infants with Robin sequence: what are we measuring? A systematic review

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Study Objectives: Identifying optimal treatment for infants with Robin sequence (RS) is challenging due to substantial variability in the presentation of upper airway obstruction (UAO) in this population. Objective assessments of UAO and treatments are not standardized. A systematic review of objective measures of UAO was conducted as a step toward evidence-based clinical decision-making for RS.

Methods: A literature search was performed in the PubMed and Embase databases (1990–2020) following PRISMA guidelines. Articles reporting on RS and UAO treatment were included if the following objective measures were studied: oximetry, polysomnography, and blood gas. Quality was appraised by the methodological index for nonrandomized studies (range: 0–24).

Results: A total of 91 articles met the inclusion criteria. The mean methodological index for nonrandomized studies score was 7.1 (range: 3–14). Polysomnography was most frequently used (76%) followed by oximetry (20%) and blood gas (11%). Sleep position of the infant was reported in 35% of studies, with supine position most frequently, and monitoring time in 42%, including overnight recordings, in more than half. Of 71 studies that evaluated UAO interventions, the majority used polysomnography (90%), of which 61% did not specify the polysomnography technique. Reported polysomnography metrics included oxygen saturation (61%), apnea-hypopnea index (52%), carbon dioxide levels (31%), obstructive apnea-hypopnea index (27%), and oxygen desaturation index (16%). Only 42 studies reported indications for UAO intervention, with oximetry and polysomnography thresholds used equally (both 40%). In total, 34 distinct indications for treatment were identified.

Conclusions: This systematic review demonstrates a lack of standardization, interpretation, and reporting of assessment and treatment indications for UAO in RS. An international, multidisciplinary consensus protocol is needed to guide clinicians on optimal UAO assessment in RS.

Keywords: obstructive sleep apnea, polysomnography, oximetry, blood gas, oxygen saturation, apnea-hypopnea index, carbon dioxide, obstructive apnea-hypopnea index, oxygen desaturation index

INTRODUCTION

Robin sequence (RS) is diagnosed in infants born with micrognathia, glossoptosis, and varying degrees of upper airway obstruction (UAO).[1] The reported birth prevalence of RS varies between 1 in 3,900 and 1 in 122,400 newborns, with a median prevalence of 1 in 14,500 newborns (6.9 per 100,000).[2]

This craniofacial anomaly is the result of a sequence of disturbances to embryonic development that is believed to begin with mandibular hypoplasia. Micrognathia can be initiated by extrinsic, intrinsic, or neurologic/neuromuscular causes.[1–4] These differing etiologies may explain the heterogeneity of the RS phenotype. Clinicians distinguish infants with syndromic RS and "RS-plus" (RS with additional malformations but without a genetically confirmed syndrome) from those without concomitant anomalies (isolated RS). A U-shaped cleft palate is a common finding in affected infants but is not required to make the diagnosis of RS.[3–5]

Because of variable degrees of breathing and feeding problems and the associated high mortality, pediatricians acknowledge that early diagnosis of RS is important.[6,7] Infants with RS can experience hypoxia and are at risk of increased work of breathing, sleep disturbance, hypercapnia, pulmonary hypertension, growth failure, and abnormal psychomotor development. Infants may be exposed to oxygen desaturation and sleep disruption that are hypothesized to contribute to neurocognitive impairment.[8,9] These breathing difficulties can range from continuous respiratory distress while awake and asleep,

necessitating immediate intervention to subtle UAO that becomes apparent only when sleeping or feeding or while in the supine position.[6,7,10]

In most infants with RS, UAO can be managed conservatively. Nonoperative interventions include prone/lateral positioning, insertion of a nasopharyngeal airway, supplemental oxygen therapy, high-flow nasal oxygen therapy, continuous or bilevel positive airway pressure, and insertion of an oral appliance (pre-epiglottic baton plate). When nonoperative treatments do not achieve respiratory stability, surgical interventions such as tongue-lip adhesion, subperiosteal release of the floor of the mouth, mandibular distraction osteogenesis, or tracheostomy could be considered.[11,12] These interventions have been investigated comprehensively; however, evaluations and metrics utilized to determine the threshold for treatment and to assess treatment outcomes are not standardized.[11,12]

Substantial variation among institutions exists for both the evaluations employed and treatments provided. Internationally accepted protocols for the investigation and management of UAO in RS are lacking.[13,14] A standardized, evidence-based approach to the assessment and treatment of UAO in infants with RS is needed. Such a protocol has the potential to guide clinicians in the timing of evaluations and indications for escalating respiratory support and to facilitate treatment comparisons across centers to improve treatment outcomes. Creation of a universal and evidence-based approach starts by standardizing the measurements used by clinicians to measure UAO, inform treatment decisions, and evaluate outcomes.

The purpose of this review was to investigate the use of objective measurements of UAO in the management of infants with RS. The measurements reviewed were selected by an international multidisciplinary RS consensus working group that included pediatricians, sleep specialists, and surgeons. Blood gas and oximetry are simple and accessible measurements to assess respiratory sufficiency and the effects of UAO. As UAO often causes obstructive sleep apnea (OSA) and polysomnography (PSG) is the recommended standard to investigate for OSA according to the American Academy of Sleep Medicine, we also included PSG in this systematic review. The review focused on how these objective measurements of oximetry, PSG, and blood gas determinations are used and interpreted as indications for treatment and evaluation of outcomes for infants with RS.

METHODS

This systematic review was performed according to PRISMA guidelines. A literature search was performed using the PubMed and Embase databases (**Figure S1** in the supplemental material; date 4-2-2020). We limited the search to publications published from 1990 onward, anticipating limited reports prior to this date. Inclusion and exclusion criteria are listed in **Figure S1.**

Two authors (RL, NC) independently assessed the full text of all studies after title abstract screening, and consensus was reached for all included studies.

The following data were extracted: publication year, country, study design, type of intervention, number of patients, mean age at intervention/admission, type of measurement, values and indices extracted from these measurements for UAO evaluation, values and indices used as indication/threshold for UAO intervention, number of patients with preintervention PSG, PSG type, monitoring time of continuous oximetry and/or PSG, position during oximetry and/or PSG, and presence and timing of postintervention and/or multiple follow-up PSGs. PSG types include type 1–4 sleep studies. Type 1 sleep studies or full PSG is the reference standard for diagnosing OSA in children.[15–20] Type 1 includes observed continuous overnight measurements of sleep and respiratory parameters with recommended signals of electroencephalography, electrooculography, and electromyography to measure sleep, and arterial oxygen saturation, a measure of carbon dioxide (transcutaneous or end tidal), nasal pressure and oronasal airflow, and abdominal and thoracic wall movements to measure breathing, with the additional recording of body position and video monitoring.[21] Type 2 studies are similar to type 1 studies but are unattended. Type 3 and type 4 studies are limited to cardiopulmonary parameters and do not include sleep parameters, with type 4 studies measuring only 1 or 2 parameters, typically oxygen saturation and heart rate.

Study quality was appraised with the methodological index for nonrandomized studies,[22] which includes a 12-item checklist. Each item is scored as 0 (not reported), 1 (reported, but inadequate), or 2 (reported and/or adequate). The maximum score is 16 for noncomparative studies and 24 for comparative studies.

For this review, UAO was defined as being independent of state (asleep or awake), while OSA was restricted to data measuring airway obstruction occurring during sleep.[23,24]

RESULTS

After the removal of duplicates, 1,123 articles were identified for title/abstract screening (**Figure S1**). Subsequently, 319 articles were selected for full text review. Of these, 62 articles were excluded due to lack of objective measurements reporting or due to lack of actual measurement data. Ninety-one studies were included in the final sample: 1 randomized controlled trial, 7 prospective studies, and 83 retrospective studies. The mean methodological index for nonrandomized studies score was 7.1 (range: 3–14) (characteristics are presented in **Table S1** in the supplemental material).

Items of the methodological index for nonrandomized studies score that demonstrated high scores included "a clearly stated aim" and "endpoints appropriate to the aim of the study" equally, followed by "inclusion of consecutive patients" and "loss to follow-up less than 5%." The item "follow-up period appropriate to the aim of the study" demonstrated low scores, followed by even lower scores of the items "prospective collection of data," "unbiased assessment of the study endpoint," and "prospective calculation of the study size."

Fifty-two studies (57%) reported on surgical interventions for UAO only, 22 studies (24%) reported on nonoperative interventions for UAO only, and 17 studies (19%) reported on a

combination of surgical and nonoperative interventions as part of a treatment algorithm.

The most common objective assessment used was PSG (76%, 69/91), followed by oximetry (20%, 18/91) and blood gas analysis (11%, 10/91). Among studies reporting the use of PSG, 36% (25/69) reported the PSG technique, and different types of techniques were observed.

A minority of studies (35%, 32/91) reported infant's position during assessment, with the supine position most frequently reported (47%), followed by the prone position (22%; **Table S1** and **Figure 1**). All reported recordings were performed in a hospital. The duration of recording was reported in 38 studies (42%), of which the majority reported an overnight period (58%, 22/38) (**Table S1**).

Treatment evaluation studies

Evaluations of UAO treatments were reported in 71 studies, which included 2,391 infants: oximetry only (6), PSG (60), PSG and blood gas analysis (4), and blood gas analysis only (1) (**Table S1** and **Figure 2**). Seventy-nine percent (56/71) of the evaluation studies reported both preintervention and postintervention data, with the threshold for treatment indicated in 31% (22/71) (**Table S1**).

Evaluation by oximetry only

Objective measurements by oximetry were reported in 6 studies that included 358 infants with RS: 5 preintervention and postintervention and 1 only preintervention. Oximetry type, specifics, and recording duration varied. In 1 study, oximetry was part of an apnea monitor, while in 3 studies oximetry was specified as continuous pulse oximetry monitoring. Values extracted from oximetry included mean/median oxygen saturation levels (4), percentage of time spent at each oxygen saturation level (1), and oxygen saturation > 90% as a binary variable (1). Two of the 6 studies reported on the position of the infant during oximetry: 1 reported the lateral or prone position, and the other reported the supine position.

Evaluation by PSG

Objective measurements assessed by some form of PSG were reported in 64 studies: 51 reported both preintervention and postintervention, 11 reported only preintervention or during intervention, and 2 reported only postintervention (**Table 1**). The PSG technique was not specified in 61% (39/64), referred to as "PSG not otherwise specified." The remaining studies provided detailed information on the PSG technique that allowed categorization according to the American Academy of Sleep Medicine: PSG type 1 or type 2 in 23% (15/64) and PSG type 3 or type 4 in 16% (10/64).

A total of 2,008 infants with RS were included in these studies, and of these, 1,699 (85%) underwent a preintervention PSG. This discrepancy is not fully explained by the intubated infant being unable to undergo a preintervention PSG; in some studies, this difference was explained by the lack of available PSG data, while others did not further specify the reason for the lack of preintervention data. In half of the studies including postintervention PSG (53%, 28/53), the time of measurement was not specified.

Oxygen saturation

Oxygen saturations assessed by oximetry as part of PSG were reported in 39 studies (61%, 39/64). The most common metric reported was lowest/minimum/nadir oxygen saturation (62%, 24/39), followed by mean oxygen saturation (41%, 16/39), percentage of time with oxygen saturation < 90% (31%, 12/39), and percentage of time with oxygen saturation > 96% (8%, 3/39 studies). Other oximetry values from PSG (percentage of time with oxygen saturation < 80%, < 85%, or < 89%; oxygen saturation < 80%; and baseline oxygen saturations) were each used in a single study (**Table 1**).

Respiratory event indices

The most frequently reported respiratory event index was the apnea-hypopnea index (AHI; 52%, 33/64), followed by the obstructive apnea-hypopnea index (27%, 17/64); the oxygen desaturation index (16%, 10/64), specified as the desaturation index to 80% in 5 studies and desaturation index to 85% in 1 study; the central apnea index (13%, 8/64); the mixed obstructive apnea index (9%, 6/64); the respiratory disturbance index (8%, 5/64); the obstructive apnea index (6%, 4/64); the hypopnea index and sleep efficiency (each 5%, 3/64); and the apnea index (3%, 2/64).

Measures of sleep disturbance were included in a small proportion of studies, including arousal index in 11% (7/64) and percentage of total sleep time characterized as rapid eye movement sleep in 8% (5/64).

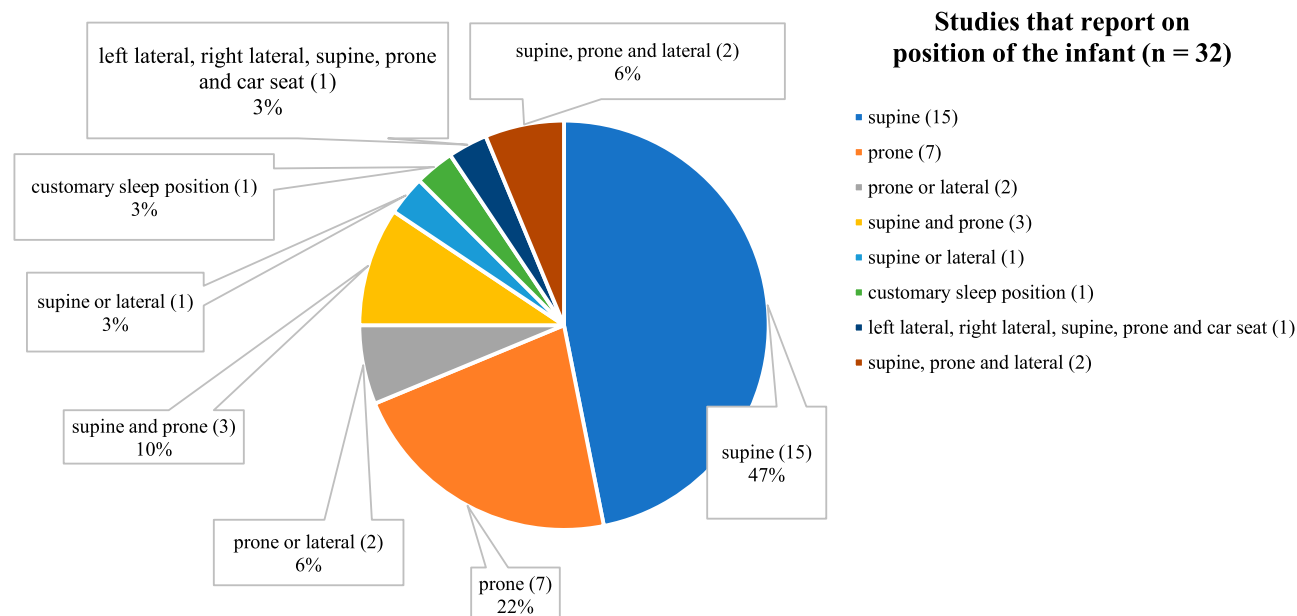## Partial pressure of carbon dioxide (pCO_2) measurement

pCO_2 measurements from PSG were reported in 20 studies (31%, 20/64). Three studies did not specify the technique of pCO_2 measurement. In 9 studies, transcutaneous pCO_2 ($tcpCO_2$) values were used: the highest $tcpCO_2$ was used in 8 studies (89%, 8/9). and the mean $tcpCO_2$ was used in 67% (6/9), and the percentage of time with $tcpCO_2$ was > 50 mm Hg in 2 studies. End-tidal (et) pCO_2 ($etpCO_2$) values were reported in the remaining 9 studies: the highest $etpCO_2$ and mean $etpCO_2$ both in 56% (5/9), the percentage of time with $etpCO_2$ > 50 mm Hg in 22% (2/9), and both the percentage of time with $etpCO_2$ > 45 mm Hg and baseline $etpCO_2$ in 1 study.

Evaluation by blood gas analysis

Blood gas values for evaluation of airway management were reported in 5 studies that included a total of 153 infants with RS. In 4 studies, blood gas analysis was specified as being from capillary blood. Values extracted included pCO_2, pH, HCO_3-, and maximum pCO_2 and HCO_3-.

Studies with indications for intervention

Objective indications/thresholds for intervention were reported in 42 studies (**Table 2** and **Figure 2**). Of these, 22 studies (52%) also used objective measurements for treatment evaluation (**Table S1**), while the remaining 20 studies only reported on indications/thresholds for intervention. Objective measurements for treatment indications/thresholds varied substantially (**Table 2** and **Figure 2**). The most common objective measurements reported were oximetry (40%, 17/42) and any form of PSG (40%, 17/42, specified according to American Academy of

Figure 1—Different positions of the infant reported in studies (n = 32).

Studies that report on position of the infant (n = 32)

- supine (15)
- prone (7)
- prone or lateral (2)
- supine and prone (3)
- supine or lateral (1)
- customary sleep position (1)
- left lateral, right lateral, supine, prone and car seat (1)
- supine, prone and lateral (2)

Sleep Medicine criteria as PSG not otherwise specified in 9 studies, PSG type 3 or type 4 in 7 studies, and PSG type 1 or type 2 in 1 study), followed by blood gas analysis and oximetry from PSG not otherwise specified (12%, 5/42 each). Of the studies that used oximetry or oximetry from PSG, the most common threshold reported was oxygen saturation < 90% for > 5% of the monitoring period (32%, 7/22). Of the studies that used any form of PSG, the most common threshold reported was an AHI > 20 events/h (41%, 7/17) to indicate surgical treatment, followed by a mixed obstructive apnea index > 3 events/h (29%, 5/17) to indicate treatment with a pre-epiglottic baton plate. A single objective metric was used to define a treatment threshold for 55% (23/42) of studies, including oxygen saturation in 11, respiratory events (AHI, mixed obstructive apnea index) in 10, and blood gas and tcpCO$_2$ in 1 study each. An additional 19% (8/42) of studies used multiple objective metrics to define treatment thresholds, with the remaining studies using a combination of objective and self-reported criteria (26%, 11/42). Twenty studies reported position, and 6 listed feeding as part of their threshold definition. In total, 34 different definitions for treatment threshold were identified (**Table 2**).

DISCUSSION

This report provides the first systematic review of the objective assessment of UAO in infants with RS. The results highlight considerable variability in the objective measures used to assess UAO and in the interpretation of these measures. PSG was the most commonly used measurement, but PSG type and interpretation of results varied. Although oximetry was less commonly used as an evaluation measure, parameters from oximetry were frequently used to define treatment thresholds

for UAO interventions. The overall quality of the evidence to support treatment decision-making for infants with RS and UAO remains low. This is emphasized by the need to exclude 19% of selected full text articles due to the lack of any objective measurement or actual data (**Figure S1**).

Of the included treatment evaluation studies, 21% did not report both preintervention and postintervention data. While availability of tests understandably varies due to resource availability, the stark lack of objective assessments and standard reporting of measures is disappointing. Measurement of airway compromise is necessary because the absence of clinical respiratory distress or snoring does not indicate the absence of airway obstruction. The latter cannot be well characterized by clinical assessment alone, and the spectrum of airway obstruction in infants with RS is broad.[25–28] The nature and severity of UAO may also change with growth or intervention.[29,30] Objective assessments of UAO, both before and after interventions, are essential to the evaluation of infants with RS and to assessing the impact of interventions, especially given the high rate of additional anomalies in RS and an associated mortality of 10%–17%.[31,32] Quantifying UAO also allows for an objective comparison of treatment modalities and builds an evidence base to assist clinicians treating UAO in infants with RS.[12] The link between OSA and long-term health and developmental consequences is well established; however, our understanding of how and why the sequelae of inadequately treated UAO and OSA manifest in RS in not clear. Although we counsel families that a primary indication for treating early airway obstruction in RS is to protect long-term brain development, we do not yet have the science to support this claim. Until we systematically assess airway obstruction, including the proposed mechanisms (oxygenation, CO$_2$ retention, sleep apnea) driving the outcomes important to patients and families, our interventions will not be based in evidence. The opportunity to link the growing body of

Figure 2—Objective measurements.
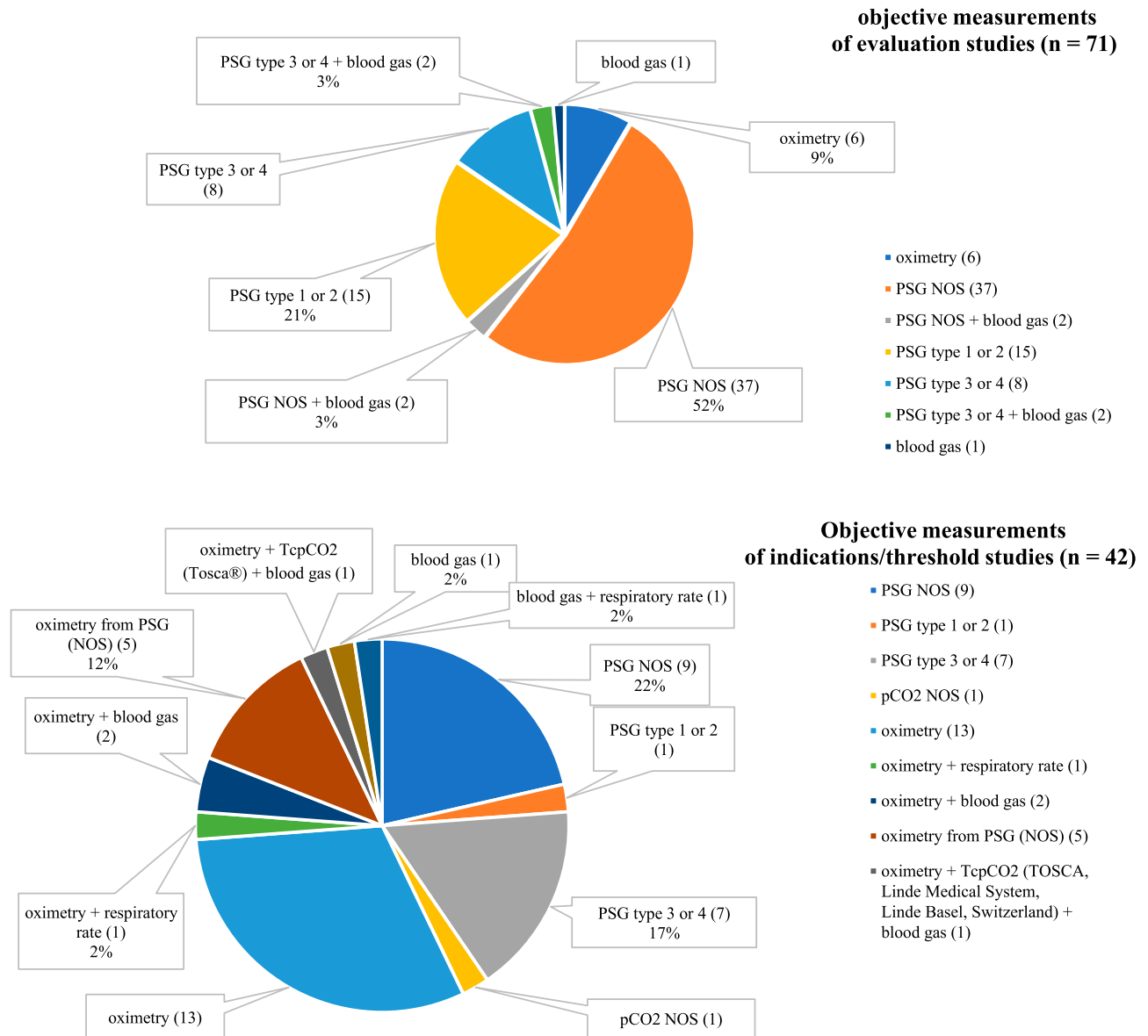
Top: Objective measurements used in all evaluation studies (n = 71). Bottom: Objective measurements used in all indications/threshold studies (n = 42). Types of PSG are categorized according to the American Academy of Sleep Medicine. pCO2 = partial pressure of carbon dioxide, PSG = polysomnography, PSG NOS = polysomnography not otherwise specified, tcpCO2 = transcutaneous pCO2.

work on longitudinal outcomes in RS with early airway and sleep assessments will be powerful in driving improvements to care.[33] The present study may serve as a starting point for future consensus recommendations for the objective measurement of UAO in infants with RS.

Although the need for objective measurement of UAO in infants with RS is apparent, we recognize that objective assessments and treatment cutoffs will vary in the absence of prospective, controlled studies of airway treatment outcomes. We do not yet know which objective criteria should be prioritized; PSG, which identifies OSA and hypoventilation but does not expose other consequences of UAO, is most commonly reported in RS.

While a type 1 PSG for the assessment of OSA is recommended in several guidelines,[15–17] infants are considered to be a complex population compared to children and therefore are excluded from consideration in all but 1 OSA guideline.[19] This, in addition to limited or no PSG access in many areas[18,34] and UAO in infants with RS occurring both asleep and awake, may account for the use of alternative objective measurements. While PSG was the most commonly reported objective measure, with specification of the signals provided for only one-third of the studies included in this review, it is unclear how many were in fact overnight, observed type 1 PSG (as specified above) rather than limited-channel studies consistent with those described as polygraphy, cardiorespiratory sleep study,

Table 1—Characteristics of studies with treatment evaluation of OSA interventions by PSG.

References	Intervention	Reported Type of Sleep Study	Type of PSG AASM	PSG Metrics	O$_2$	CO$_2$	Infant Position	Monitoring Time	Preintervention and/or Postintervention	Workup PSG
Surgical interventions										
Resnick et al, 2019[14]	TLA/MDO	PSG	PSG NOS	AHI, arousal index, % REM sleep	Lowest O$_2$ saturation, % time O$_2$ saturation 96%–100%	—	Supine	—	Pre and post	Post
Zhang, 2019	MDO	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	Mean 211 d (± 233 d)
Heffernan et al, 2019	MDO	PSG	Type 1	AHI, arousal index, % REM sleep	Lowest O$_2$ saturation, % time O$_2$ saturation > 96%	—	—	—	Pre and post	Post
Gary et al, 2018	MDO	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	Post
Fahradyan et al, 2018	MDO/(Consv.=PP + sup. O$_2$)	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	Post
Hammoudeh et al, 2018	MDO	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	2.3 mo and 2.9 y
Broucqsault et al, 2018	TLA	PSG	PSG NOS	AHI	O$_2$ saturation	Mean pCO$_2$ (NS)	—	Nap PSG (NS)	Pre and post	1 mo
Mermans et al, 2018	TLA	PSG	Type 2	OAHI, ODI	—	—	—	Overnight	Pre and post	Post
Biskup et al, 2017	MDO	PSG	PSG NOS	Obstructive index	—	—	—	—	Pre and post	Post
Ramieri et al, 2017	FEMOD	PSG	PSG NOS	AHI	—	—	—	—	Post	Post
Zellner et al, 2017	MDO	PSG	PSG NOS	OAHI	—	—	—	Overnight	Pre and post	Post
Bangiyev et al, 2016	MDO	PSG	PSG NOS	AHI, OAHI, mixed AHI, central AHI, REM-sleep to NREM-sleep ratio	Lowest O$_2$ saturation, % time O$_2$ saturation < 90%	—	—	—	Pre and post	Post
Resnick et al, 2016	TLA	PSG	PSG NOS	AHI, arousal index, % REM sleep	Lowest O$_2$ saturation, % time O$_2$ saturation > 96%	—	Supine and prone	—	Pre and post	Mean 57 d
Greathouse et al, 2016	MDO/TLA	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	1 mo and 1 y
Ching et al, 2015	MDO	MPAS	Type 1/2	AHI	—	—	Left lateral, right lateral, supine, prone, and in a carseat position (if available)	—	Pre	—
Tahiri et al, 2015	MDO	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	1 mo and 1 y
Goldstein et al, 2015	MDO	PSG	Type 1	OAHI, arousal index, % REM sleep, sleep efficiency	Lowest O$_2$ saturation, % time O$_2$ saturation < 90%	Highest etpCO$_2$, mean etpCO$_2$, % time etpCO$_2$ > 50 mm Hg, highest tcpCO$_2$, mean tcpCO$_2$	—	Overnight	Pre and post	Post
Tholpady et al, 2015	MDO	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	Post
Cascone et al, 2014	FEMOD	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	Post
Murage et al, 2014	MDO	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	Post
Flores et al, 2014	MDO/TLA	PSG	PSG NOS	AHI	O$_2$ saturation	—	—	—	Pre and post	1 and 12 mo
Papoff et al, 2013	MDO/TLA	PSG	PSG NOS	AHI	O$_2$ saturation	—	—	—	Post	Post
Sedaghat et al, 2012	TLA	PSG	Type 1	OAHI, OAI, HI, CAI, MAI, RDI	Lowest O$_2$ saturation	Mean etpCO$_2$	—	Overnight	Pre and post	17 d (range: 5–32 d)
Caouette-Laberge et al, 2012	SPRFM	PSG	PSG NOS	AHI	% time O$_2$ saturation < 90%	—	—	—	Pre and post	Post and age 1 y

(continued on following page)

Table 1—Characteristics of studies with treatment evaluation of OSA interventions by PSG. (continued)

References	Intervention	Reported Type of Sleep Study	Type of PSG AASM	PSG Metrics	O_2	CO_2	Infant Position	Monitoring Time	Preintervention and/or Postintervention	Workup PSG
Hammoudeh et al, 2012	MDO	PSG	Type 1	OAHI	Lowest O_2 saturation, baseline O_2 saturation, % time O_2 saturation < 90%	Baseline CO_2, highest etpCO_2	Customary sleep position	Daytime nap or overnight	Pre and post	Post
Hong et al, 2012	MDO	Sleep study	PSG NOS	AHI	Lowest O_2 saturation	—	—	—	Pre	—
Cheng et al, 2011	MDO plus TLA	PSG	PSG NOS	RDI, RDI in REM sleep	Lowest O_2 saturation, % time O_2 saturation < 90%	Highest pCO_2 (NS)	Prone	—	Pre and post	Post and 9 mo–6 y
Mohamed et al, 2011	MDO	PSG	PSG NOS	RDI	O_2 saturation	—	—	—	Pre and post	Post
Anderson et al, 2011[25]	Prior to surgical intervention (NS)	PSG	Type 1	OAHI, OAI, HI, RDI	Lowest O_2 saturation	Highest etpCO_2	—	Overnight	Pre	—
Looby et al, 2009	MDO	PSG	PSG NOS	AHI	Lowest O_2 saturation	—	—	—	Pre and post	Post
Neto et al, 2009	PP/MDO plus TRACH	PSG	PSG NOS	AHI	—	—	—	—	Pre	—
Gifford et al, 2008	MDO	PSG	PSG NOS	OAHI	—	—	—	—	Pre and post	2–4 mo
Mitsukawa et al, 2007	MDO	PSG	PSG NOS	AHI	O_2 saturation	—	—	—	Pre and post	1–2 mo
Burstein et al, 2004	MDO	Sleep study	PSG NOS	RDI	Lowest O_2 saturation	—	—	—	Pre and post	Post
Monasterio et al, 2004	MDO	PSG	PSG NOS	AI, HI, RI	O_2 saturation	—	Supine	8 h	Pre and post	2–4 mo
Wittenborn et al, 2004	MDO	PSG	Type 3/4	OAI	O_2 saturation	—	—	—	Pre and post	3 mo
Hoffman, 2003	TLA	Sleep study	PSG NOS	—	O_2 saturation, lowest O_2 saturation	Mean tcpCO_2, highest tcpCO_2	—	—	Pre and post	3 days post and discharge
Morovic et al, 2000	MDO	PSG	PSG NOS	AI	O_2 saturation < 80%	—	—	12 h	Pre and post	Post
Conservative interventions										
Hong et al, 2020 (42)	PP	PSG	Type 1	OAHI, CAI, arousal index, sleep efficiency	Lowest O_2 saturation	Highest etpCO_2	Nonprone (supine, left, right) and prone	Overnight	During	—
Ehsan et al, 2019 (44)	Consv. (watchful waiting or sup. O_2)	PSG	Type 1	AHI, OAHI, CAI, arousal index, sleep efficiency, % REM sleep, % NREM sleep	Lowest O_2 saturation	Mean etpCO_2	Supine	Overnight	Pre and post	< 12 mo
Ho et al, 2019	PEBP	PSG	PSG NOS	AHI	Lowest O_2 saturation, % TST O_2 saturation < 90%	Mean tcpCO_2	—	Overnight	Pre and post	6 mo
Wiechers et al, 2019	PEBP	CRSS	Type 3	MOAI, desaturation index (DI80)	—	—	Supine	Evening, minimum 8 h	Pre and post	Discharge and 3 mo
Coutier et al, 2019 (40)	PP	PSG	Type 1/2	OAHI, OAI, OHI, CAI, MAI, ODI 3%, ODI 4%, arousal index, sleep efficacy %, sleep efficiency %	O_2 saturation, % TST O_2 saturation < 90%	Highest tcpCO_2, mean tcpCO_2, % time with tcpCO_2 > 50 mm Hg	Supine and prone	Overnight	During	—
Muller-Hagendorn et al, 2017	PEBP	Sleep study	Type 3	MOAI, desaturation index (DI80)	—	—	Supine	Evening, minimum 8 h	Pre and post	In situ: 2 days PEBP, in situ 3 mo after discharge
Poets et al, 2017	PEBP	CRSS	Type 3	MOAI, desaturation index (DI80)	—	—	Supine	Evening, minimum 8 h	Pre and post	Discharge and 3 mo
Buchenau et al, 2017	PEBP	CRSS	Type 3	MOAI, desaturation index (DI80)	—	—	Supine	Evening, minimum 8 h	Pre and post	Discharge and 3 mo
Albino et al, 2016	Sup. O_2 (nasal cannula/NPA/intubation)	PSG	PSG NOS	AHI	% TST O_2 saturation < 90%	—	Prone	—	During	—

(continued on following page)

Table 1—Characteristics of studies with treatment evaluation of OSA interventions by PSG. (continued)

References	Intervention	Reported Type of Sleep Study	Type of PSG AASM	PSG Metrics	O_2	CO_2	Infant Position	Monitoring Time	Preintervention and/or Postintervention	Workup PSG
Adeleye et al, 2016	PAP	PSG	Type 1	AHI	O_2 saturation, lowest O_2 saturation, % time O_2 saturation < 90% and < 80%	Mean etpCO$_2$, % time mean etpCO$_2$ > 50 mm Hg	—	Overnight	Pre	—
Amaddeo et al, 2016	PP/CPAP/TRACH	PG	Type 3/4	AHI, ODI	Lowest O_2 saturation	Highest tcpCO$_2$	Prone	Daytime nap PG (NS)	Pre	—
Kimple et al, 2014 (41)	PP	PSG	Type 1	OAHI, CAI	Lowest O_2 saturation	Highest etpCO$_2$	Supine and prone	Overnight	Pre and post	Post positioning
Girbal et al, 2014	NIV: CPAP/BPAP	CRS & PSG	PSG NOS	AHI	O_2 saturation	—	—	—	Pre and during	In situ
Bacher et al, 2011	PEBP	PG	Type 3	MOAI, CAI, ODI	—	—	Supine	Evening, minimum 8 h	Pre and post	Discharge and 3 mo
Leboulanger et al, 2010	NRS/(TRACH)	PS	Type 4	—	O_2 saturation, lowest O_2 saturation, % time O_2 saturation < 90%	Mean tcpCO$_2$, highest tcpCO$_2$, % time tcpCO$_2$ > 50 mm Hg	—	5 min during nocturnal sleep, after spontaneous breathing period of 15 min	Pre and during	In situ
Buchenau et al, 2007	PEBP	CRSS	Type 3	MOAI, CAI, desaturation index DI85 & DI80	—	—	Supine	Evening, minimum 8 h	Pre and post	After 36 h
Chang et al, 2000	NPA	PSG	Type 1	—	O_2 saturation	Mean tcpCO$_2$	—	Overnight	Pre, during, and post	In situ and 5–17 mo post NPA removal
Wilson et al, 1999	O_2/CPAP/NPA	PSG	PSG NOS	—	O_2 saturation	—	—	—	Pre and post	Post
Combination of interventions										
Hicks et al, 2018	Consv. (sup. O_2/PP/NPA)/MDO/TLA/TRACH	PSG	PSG NOS	AHI	Lowest O_2 saturation, % time with O_2 saturation < 89%	Highest pCO$_2$, % time with pCO$_2$ > 50 mm Hg (NS)	—	Overnight	Pre and post	Post
Runyan et al, 2018	PP/MDO/TRACH	PSG	PSG NOS	AHI, OAHI	—	—	—	—	Pre and post	Post
Khansa et al, 2017	PP or SP/MDO/TLA	PSG	PSG NOS	AHI	—	—	—	—	Pre and post	MDO: 83 d and TLA: 67 d and PP: 90 d
Lee et al, 2015[30]	Consv./MDO/TLA/TRACH/SGP	PSG	Type 1	AHI, OAHI, CAI	Lowest O_2 saturation, % time O_2 saturation < 90%	Highest tcpCO$_2$	Supine or lateral	—	Pre and post	Mean 241 d
Van Lieshout et al, 2014	PP/respiratory support (NPA, CPAP, and/or O_2 sup.)/TRACH + MDO	PSG	PSG NOS	OAHI	—	—	—	Overnight	Pre	—
Daniel et al, 2013	PP/CPAP/MDO	PSG	Type 1/2	AHI, OAHI, OAHI during REM sleep, OAHI during SW or quiet sleep	O_2 saturation, lowest O_2 saturation	Highest tcpCO$_2$	—	Minimum 4 h sleep	Pre	—
Abel et al, 2012	PP/NPA/TRACH	PSG	PSG NOS	Number of clusters of desaturations	Lowest O_2 saturation	—	—	Overnight	Pre and post	2-mo intervals in situ and post NPA removal
Bull et al, 1990	O_2/TLA/TRACH	PSG	Type 3	% TST obstructive apnea > 6 s	O_2 saturation, % time O_2 saturation < 90% and < 85%	Mean etpCO$_2$, % time etpCO$_2$ > 45 mm Hg	Lateral, supine, prone	Spontaneous sleep and wakefulness, mean 2 h	Pre and post	TLA/TRACH: post and O_2: 3 mo

For all references, please see supplemental material. AASM = American Academy of Sleep Medicine, AHI = apnea-hypopnea index, AI = apnea index, BPAP = bilevel positive airway pressure, CAI = central apnea index, Consv. = conservatively, CPAP = continuous positive airway pressure, CRS = cardiorespiratory study, CRSS = cardiorespiratory sleep study, DI80 = desaturation index defined as events < 80% O_2 desaturation per hour TST, DI85 = desaturation index defined as events < 85% O_2 desaturation per hour TST, etpCO$_2$ = end-tidal pCO$_2$, FEMOD = fast early mandibular osteogenesis distraction, HI = hypopnea index, MAI = mixed apnea index, MDO = mandibular distraction osteogenesis, MOAI = mixed obstructive apnea index, MPAS = multipositional airway study, NIV = noninvasive ventilatory support (both CPAP or BPAP), NPA = nasopharyngeal airway/tube, NOS = not otherwise specified, NREM = nonrapid eye movement, NRS = noninvasive respiratory support (both CPAP and PAP), NS = not specified, OAHI = obstructive apnea-hypopnea index, OAI = obstructive apnea index, ODI = oxygen desaturation index, OHI = obstructive hypopnea index, PAP = positive airway pressure, pCO$_2$ = partial pressure of carbon dioxide, PEBP = pre-epiglottic baton plate/Tubingen plate, PG = polygraphic study, Post = post intervention not specified, PP = prone positioning, PS = physiologic study, PSG = polysomnography, RDI = respiratory disturbance index, REM = rapid eye movement, SGP = supraglottoplasty, SP = side positioning, SPRFM = subperiosteal release of the floor of the mouth, sup. = supplemental, SW = slow wave, tcpCO$_2$ = transcutaneous pCO$_2$, TLA = tongue-lip adhesion, TRACH = tracheostomy, TST = total sleep time.

Table 2—Characteristics of studies reporting on treatment indicators/thresholds for OSA interventions.

Study	Intervention	Objective Measurements	Position of the Infant	Monitoring Time	Indication/Threshold
Surgical interventions					
Konofaos et al, 2019	MDO	PSG (NOS)	Supine	—	1) severe upper airway obstruction that was not adequately managed with conservative therapy, 2) O_2 saturation < 80% while lying supine, 3) AHI ≥ 20 events/h, and (4) poor weight gain
Zhang et al, 2019	MDO	Oximetry	—	—	Clusters of desaturation with at least 3 dips < 80%
Ching et al, 2015	MDO	PSG type 1/2 (MPAS)	Left lateral, right lateral, supine, and prone position and in a carseat (if available)	—	AHI > 5 events/h
Tahiri et al, 2015	MDO	PSG (NOS)	—	—	AHI > 20 events/h or significant CO_2 retention (NS) and no central sleep apnea present
Greathouse et al, 2015	MDO/TLA	PSG (NOS)	—	—	AHI > 20 events/h or CO_2 retention with abnormal PSG (NS) or worsening of clinical status after exclusion of other sources of airway obstruction
Flores et al, 2015	MDO	PSG (NOS)	—	—	AHI > 20 events/h or significant CO_2 retention (NS) and no central sleep apnea
Tholpady et al, 2015	MDO	PSG (NOS)	—	—	AHI > 20 events/h or significant CO_2 retention (NS) and failure of nonoperative interventions
Flores et al, 2014	MDO/TLA	PSG (NOS)	—	—	MDO: AHI ≥ 20 events/h or significant CO_2 retention (NS), absence of other significant airway anomalies as demonstrated by laryngoscopy/bronchoscopy, and absence of temporomandibular joint abnormality
Murage et al, 2014	MDO	PSG (NOS)	—	—	AHI > 20 events/h or significant CO_2 retention (NS) and no central sleep apnea
Dong et al, 2014	Mandibular traction	Oximetry	Lateral or prone	24 h	Mean O_2 saturation < 90% (24 h) in the lateral/prone position, or if O_2 saturation decreased continuously due to dyspnea during the monitoring period and manual intervention/rescue was required
Breugem et al, 2012	MDO	Oximetry	—	12 h	O_2 saturation < 90% for > 5% of 12 h
Sesenna et al, 2012	MDO	Oximetry, respiratory rates	—	—	Repeated apneic episodes with severe desaturation (70%) and respiratory rate higher than 60/min
Baciliero et al, 2011	Mandibular traction	Oximetry	—	24 h	Desaturation (during the following activities of early life: sleeping, feeding, or wakefulness): O_2 saturation < 90% for ≥ 5% observation time (neonates at least 24 h, children during sleep) or single recorded value of O_2 saturation of < 80%
Kolstad et al, 2011	MDO	CO_2 measurement (NOS)	—	—	Severe obstruction: persistent pCO2 > 50 mm Hg or a life-threatening event related to upper airway compromise
Miloro et al, 2010	MDO	Oximetry	—	—	Frequent apneic episodes with O_2 saturation < 70% on room air with repeat apnea monitor triggering
Shen et al, 2009	MDO	Oximetry	Prone	—	O_2 saturation of about 40% in prone position
Breugem et al, 2008	SPRFM	Oximetry	—	24 h	O_2 saturation < 93% for > 95% per 24 h, elevated CO_2 retention levels (NS)
Denny, 2004	MDO	Oximetry from PSG (NOS)	—	-	Repeated O_2 desaturations < 80% and no spontaneous correction, abnormal PSG (NS)
Morovic et al, 2000	MDO	PSG (NOS)	—	12 h	AHI > 20 events/h and O_2 saturation < 80% during or within 12 h after examination
Gilhooly et al, 1993	TLA	Oximetry from PSG (NOS)	Prone position except when feeding and other nursing care	—	Significant episode of airway obstruction: an event lasting 15 seconds or more during sleep or quiet activity or shorter episodes of obstruction associated with a decrease in heart rate to < 80 beats per min and/or a drop in O_2 saturation to < 85%
Conservative interventions					
Wiechers et al, 2019	PEBP	PSG type 3 (CRSS)	Supine	Evening, minimum 8 h	MOAI > 3 events/h
Müller-Hagendorn et al, 2017	PEBP	PSG type 3 (sleep study)	Supine	Evening, minimum 8 h	MOAI > 3 events/h
Poets et al, 2017	PEBP	PSG type 3 (CRSS)	Supine	Evening, minimum 8 h	MOAI > 3 events/h
Amaddeo et al, 2016	CPAP	PSG type 3/4 (PG)	Prone	Daytime nap PG (NS)	AHI > 10 events/h and/or minimal O_2 saturation < 90% and/or tcpCO2 > 50 mm Hg and/or ODI > 15 events/h
Albino et al, 2016	Supplemental O2 (nasal cannula/NPA/intubation)	Oximetry from PSG (NOS)	Prone	—	Persistent episodes of respiratory distress: 10% O_2 desaturation ≥ 10 s at rest, while sleeping, or during feeding
Bacher et al, 2011	PEBP	PSG type 3 (PG)	Supine	Evening, minimum 8 h	MOAI > 3 events/h; contraindication: OSA-related severe hypoxemia, defined as 3 or more desaturation events to < 60% O_2 saturation
Leboulanger et al, 2010*	NRS: CPAP or noninvasive positive pressure ventilation/TRACH	PSG type 4 (PS)	—	—	tcpCO2 > 50 mm Hg for > 10 consecutive min and/or > 10% of sleep time despite positioning measures and exclusive nasogastric tube feeding. For some patients, NRS was initiated in the PICU because they were not able to breathe spontaneously without a pharyngeal tube for > 30 min without profound decreases in pulse O_2 saturation (< 80%) and hypercapnia (tcpCO2 > 60 mm Hg).
de Buys Roessingh et al, 2007	(PP)†/NPA	Oximetry, blood gas	Supine (slowly lowering the child while sleeping into supine position, repeated while bottle-feeding)	—	Persistent desaturation < 90% with clinical evidence of respiratory distress or CO_2 retention as evidenced by a base excess of > 6.5

(continued on following page)

Table 2—Characteristics of studies reporting on treatment indicators/thresholds for OSA interventions. (continued)

Study	Intervention	Objective Measurements	Position of the Infant	Monitoring Time	Indication/Threshold
Anderson et al, 2007	NPA	Oximetry	Supine (gently lowered into a supine position while sleeping; if no obstruction then this was repeated while bottle-feeding)	24–36 h	O_2 saturation < 90% for > 5% (period: 24 to 36 h) or intermittent deeper episodes of desaturation < 80%
Buchenau et al, 2007	PEBP	PSG type 3 (CRSS)	Supine	Evening, minimum 8 h	MOAI > 3 events/h; contraindication: additional major malformations (eg, congenital heart disease), a concomitant upper or lower respiratory tract infection, or severe UAO-related hypoxemia (ie, > 3 desaturations to < 60% O_2 saturation)
Wagener et al, 2002	NPA	Oximetry	Supine (gently lowered into a supine position while sleeping; if no obstruction then this was repeated while bottle-feeding)	24–36 h	O_2 saturations < 90% for > 5% of the time (period of 24–36 h) or deep desaturations < 80%
Combination of surgical and conservative interventions					
Runyan et al, 2018	(PP)/MDO/(TRACH)†	PSG (NOS)	—	—	Surgical intervention should be considered at an OI > 20 (combined with other examination findings)
Li et al, 2017	(PP)†/ TLA/MDO/ FMR/TRACH	Oximetry	Prone	—	Surgical intervention for patients with ongoing desaturations with PP (part of treatment algorithm). Patients were defined as having desaturations if any single recorded hospital O_2 saturation was < 80% or if more than 1 hospital oxygen saturation was < 90%.
Paes et al, van Nunen, Speleman, et al, 2015[39]	PP/NPA/TLA/ MDO/TRACH	Oximetry, tcpCO2 (TOSCA-Linde Medical System, Basel, Switzerland) blood gas	Prone or lateral	—	Moderate/severe UAO (as part of treatment algorithm): (1) O_2 saturations of < 90% for > 5% of the monitored time and/or any single desaturation < 80%, (2) Blood gas analysis revealing respiratory acidosis (pCO_2 > 50 mm Hg, HCO_3^- > 30 mm Hg), or $tcpCO_2$ > 50 mm Hg during > 25% of the TST.
Salmen et al, 2015	(PP)†/NPA/TRACH	Oximetry	—	—	Severe RS: recurrent crises of pallor and/or cyanosis and/or apnea, intercostal and supraclavicular retractions, O_2 saturation < 90% with an O_2 requirement to improve this condition, and severe feeding difficulties for which feeding tubes were necessary
Abel et al, 2013	(PP)/NPA/(TRACH)†	Oximetry from PSG (NOS)	—	Overnight	NPA: if the PSG indicated moderate or severe obstruction (if the child was clinically severely obstructed on admission, an NPA was inserted without a preintervention sleep study). Moderate UAO: a set of at least 3 clusters of desaturations with at least 3 dips < 85% (but not < 80%). Severe UAO for a set of at least 3 clusters of desaturations with at least 3 dips < 80%.
Glynn et al, 2011	(PP)/NPA/(TRACH)†	Oximetry	Supine (gently lowered into a supine position while sleeping; if no obstruction then this was repeated while bottle-feeding).	24–36 h	O_2 saturations < 90% for > 5% of the time (24–36 h)
Pradel et al, 2009	(PP or SP/palatal plate)†/ mandibular traction	Oximetry, blood gas	—	—	pCO_2 > 60 mm Hg, pH < 7.2, and O_2 saturations < 85%
Schaefer et al, 2004	(PP)†/MDO/ TLA/TRACH	Oximetry from PSG (NOS)	—	12 h	Patients are defined as having desaturations (part of treatment algorithm): if any single O_2 saturation value is < 80% or if O_2 saturation values < 90% for 5% or more of the monitored time (minimum of 12 h for neonates or during sleep for older children). Patients without evidence of desaturation undergo further monitoring with a sleep study (continuous monitoring of O_2 saturation, $etpCO_2$ levels, and electroencephalographic output).
Marques et al, 2001	(NPA)†/TLA/TRACH	Oximetry	Supine	—	Unable to maintain O_2 saturation > 90% with NPA in situ and unimproved oral acceptance of food
Caouette-Laberge et al, 1994[38]	(PP/NPA)†/SPRFM	Blood gas	—	—	pO_2 < 60 mm Hg or pCO_2 > 50 mm Hg
Augarten et al, 1990	(PP)†/TLA	Blood gas, respiratory rates	Prone	—	Failure of following criteria: respiratory rate < 60 + pCO_2 < 60 mm Hg + pO_2 > 65 mm Hg (blood gas) + oxygen requirement < 60%

For all references, please see supplemental material. *Different monitoring time (not specified) for treatment threshold compared to monitoring time for treatment evaluation. †If multiple interventions were reported in a study, but indication/threshold was only reported for 1 certain intervention, then the other interventions are demonstrated between parentheses. AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, CRSS = cardiorespiratory sleep study, $etpCO_2$ = end-tidal pCO_2, FMR = floor of mouth release, MDO = mandibular distraction osteogenesis, MOAI = mixed obstructive apnea index, MPAS = multipositional airway study, NOS = not otherwise specified, NPA = nasopharyngeal airway/tube, NRS = noninvasive respiratory support (both CPAP and PAP), NS = not specified, ODI = oxygen desaturation index, OI = Obstructive Index, OSA = obstructive sleep apnea, pCO_2 = partial pressure of carbon dioxide, PEBP = pre-epiglottic baton plate/Tubingen plate, PG = polygraphic study, PICU = pediatric intensive care unit, pO_2 = partial pressure of oxygen, PP = prone positioning, PS = physiologic study, PSG = polysomnography, SP = side positioning, SPRFM = subperiosteal release of the floor of the mouth, $tcpCO_2$ = transcutaneous pCO_2, TLA = tongue-lip adhesion, TRACH = tracheostomy, UAO = upper airway obstruction.

Table 3—List of minimal reporting for OSA treatment studies using PSG in infants with RS.

1. Indication for preintervention PSG
2. Age, mo, at PSG
3. Body position (supine, side, prone, supine/side, supine/prone, supine/side/prone)
4. Time of day and duration of PSG recording
5. Equipment setup, including specific channels (AASM, other—specify reference or describe protocol)
6. Scoring protocol OSA (AASM, other—specify reference or describe protocol)
7. Thresholds that guide intervention decision (if applicable, specify measures and cutoff)
8. Age, mo, postintervention PSG to investigate treatment success

AASM = American Academy of Sleep Medicine, OSA = obstructive sleep apnea, PSG = polysomnography, RS = Robin sequence.

cardiorespiratory study, multipositional airway study, and physiological study (**Table S1**). The lack of information on the specific signals for individual studies or classification according to the American Academy of Sleep Medicine impaired our ability to compare or combine the outcomes of intervention studies. This review highlights the wide range in measurement techniques used and emphasizes the importance of clear documentation, if not standardization, of these variables in future studies assessing UAO and OSA in infants with RS. Based on the results of this review, a list of minimal reporting for future treatment studies using PSG in infants with RS is given in **Table 3.**

There is also considerable variability in the parameters used to define OSA in infants with RS, even within studies using the same objective measurements. We identified 34 different definitions of a treatment threshold. This may be attributable to the lack of accepted criteria for the diagnosis of OSA in infants. The limited normative PSG data available from healthy infants support that current pediatric criteria, where OSA is present if the AHI is ≥ 2 events/h or the obstructive apnea-hypopnea index is ≥ 1 event/h,[19] are not appropriate for neonates and infants. Respiratory event rates are higher in infants with an AHI ranging from 1–38 events/h and an obstructive apnea index ranging from 0.2–12.5 events/h at age < 30 days,[35] with an AHI ranging from 1.9–46.4 events/h and a mixed obstructive AHI range of 0.2–7.0 events/h at age 3 months[36] and an obstructive apnea-hypopnea index range of 0.5–5.5 events/h at age 3–4 months.[27] This pattern of a decreasing number of respiratory events in healthy infants holds true at high altitudes, where the total number of respiratory events is higher than at lower altitudes,[37] suggesting that thresholds for defining OSA in infancy need to account for changes in respiratory events by age. While defining OSA by respiratory events above the upper limit for healthy infants alone may be insufficient to identify those at risk for negative outcomes, using pediatric PSG criteria in infants leads to overestimation of OSA compared to a diagnosis by expert sleep physicians.[24] To avoid inaccurate diagnosis, there is a need to establish criteria to objectively identify OSA in infants with RS that account for age-related changes in respiratory events. Ideally, thresholds will be based on a combination of normative data and the relationship of respiratory event rates to important health outcomes such as growth, feeding, quality of life, and neurocognitive function specific to this high-risk population.

These longer-term outcomes will ultimately be the evidence to guide early treatment decisions.

The majority of studies included in this review evaluated only surgical interventions for UAO. This is surprising as surgical interventions are indicated in the minority of infants with severe OSA.[6,7,19,38,39] In alignment with the ethical obligation "primum non nocere," the least-invasive, effective interventions must be considered. It is possible that first-line treatment for infants with mild UAO may be side-lying or prone positioning, with minimal objective evaluation if this is successful in supporting breathing during sleep and feeding. Three studies used PSG to estimate the effect of prone positioning and demonstrated that it did not completely resolve OSA in the majority of infants. Therefore, routine PSG evaluation in individual infants undergoing prone positioning as a definitive treatment is recommended,[40–42] although questions remain whether prone positioning can be recommended in all infants.[43] The natural history of early-infant OSA has not been well studied. In a large cohort of 162 infants with RS, 21 infants who were treated conservatively (watchful waiting or supplemental oxygen) experienced resolution of OSA confirmed by PSG at a median age of 15 months.[44]

Outcome assessments are also limited for other conservative treatments, including the effect of nasopharyngeal airway, noninvasive ventilation, and orthodontic appliances (eg, pre-epiglottic baton plate) on objective measures of UAO, independently and in comparison to other intervention(s). Future studies focused on objective evaluation of these conservative interventions to either confirm complete resolution of UAO or to indicate additional interventions are needed. An important result would be valid comparisons of nonoperative to operative interventions. To achieve this, at a very minimum, treatment studies must provide standardized reporting on metrics and transparency on the treatment protocols employed. These standards will facilitate improved practice, allowing clinicians to be armed with more accurate information to aid counseling on the risks and benefits of the full spectrum of treatments for UAO in RS. Pediatricians and neonatologists serve an essential role in recognizing UAO in infants with RS and will rely on these improved tools to guide clinical decision-making.

There are limitations of this systematic review that must be acknowledged. The included studies were primarily retrospective with only 1 randomized trial and 7 prospective studies. This limits the included studies to those with low methodological

quality (methodological index for nonrandomized studies score) and a serious risk of bias. The focus of this systematic review was not on treatment outcomes of the included intervention studies. However, missing data on variables such as position (65%), monitoring time (58%), PSG technique (61%), and time of postintervention PSG (53%) also contribute to a serious risk of bias. With incomplete reporting of these variables, age-related changes in sleep and breathing between the preintervention and postintervention measurements are important confounders to consider. The search focused on 3 objective assessments of UAO used commonly in practice by pediatricians, neonatologists, and craniofacial specialists and did not include all potential measures of UAO. Finally, the current review did not assess feeding difficulties; however, UAO and feeding problems are closely related in infants with RS.

CONCLUSIONS

This systematic review demonstrates a lack of standardized use, implementation, and interpretation of objective measurements in the assessment of UAO resulting in OSA in infants with RS. A wide variation was observed in the use, interpretation, and reporting of these values. Until measures and metrics are systematically assessed and reported, front-line physicians rely on limited evidence and practice variation persists. Future work is needed to establish accepted definitions of the presence and severity of UAO and OSA in infants with RS. Clear reporting of objective measurement techniques to assess airway obstruction, guide decision-making, and evaluate outcomes is necessary in this high-risk population. To build a valid and useful evidence base, assessments of UAO and treatment in infants with RS should be assessed alongside long-term and patient-centered outcomes in this population.

ABBREVIATIONS

AHI, apnea-hypopnea index
etpCO$_2$, end-tidal pCO$_2$
OSA, obstructive sleep apnea
pCO$_2$, partial pressure of carbon dioxide
PSG, polysomnography
RS, Robin sequence
tcpCO$_2$, transcutaneous pCO$_2$
UAO, upper airway obstruction

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DISCLOSURE STATEMENT