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Contents

A Joint Effort on Children with Obstructive Apnea by Asian Pediatric Pulmonologists

Obstructive sleep apnea syndrome (OSAS) is a relatively common disease that affects 1%–5% of prepubertal children. While standard management guideline has been developed for the use in developed countries in the USA and Europe, management of childhood OSAS in Asia has not been standardized. In the current issue of *Pediatric Respirology and Critical Care Medicine*, Ng *et al.* published a position statement on behalf of the Asian Paediatric Pulmonology Society (APPS) for management of children with OSAS in Asia based on the expert panel convened by APPS. This up-to-date statement covered the most important issues of OSAS regarding diagnosis, conservative treatment, adenotonsillectomy, orthodontic treatment, and orofacial myofunctional therapy. This report also witnesses the joint effort of pediatric pulmonologists in Asia to achieve a consensus for the care of children with OSAS. I am sure that this position statement provides a useful guide for the primary pediatricians, pediatric pulmonologists, and pediatric sleep specialists.

Nathan reported the findings of a prospective study on the relationship between viral infection in lower respiratory infection and hospitalization for children below 2 years of age who visited the emergency department of a tertiary general hospital in Kuala Lumpur, Malaysia. The authors found that female sex, nursery attendance, and lack of breastfeeding were significantly associated with admissions but not viral infection. The most common viruses identified in the emergency department were respiratory syncytial virus (RSV), human rhinovirus, and parainfluenza virus in the study. This study confirmed the importance of RSV even in tropical climate.

In the review of clinical aspects of pediatrics OSAS, Guilleminault *et al*. reviewed the historical developments of recognition of OSAS. Then, they summarized the physiology of upper airway collapse during sleep. The authors emphasized the variable presenting complaints at different ages of children with OSAS. Accurate diagnosis is the key to successful treatment of OSAS; the level of airway obstruction should be vigilantly looked for. Finally, the pathogenesis of OSA due to orofacial growth at young age, related to the functioning of sucking, swallowing, speech development, and nasal breathing, were emphasized. To decrease morbidity of pediatric patients with obstructive sleep apnea, early recognition and timely treatment remains the goal of therapeutic management.

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Review Article

The Asian Paediatric Pulmonology Society (APPS) Position Statement on Childhood Obstructive Sleep Apnea Syndrome

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Abstract

With recognition of the importance of obstructive sleep apnea syndrome (OSAS) in children, practice guidelines have been developed for the management of OSAS in the USA and Europe. A panel of experts in pediatric OSAS in Asia were appointed by the Asian Paediatric Pulmonology Society (APPS) to prepare a position statement for management of childhood OSAS in Asia. The purpose of this statement is to provide a reference standard in the diagnosis and management of childhood OSAS for doctors working in Asia. The expert panel determined the scope of this statement. Focused literature search related to the key topics was conducted by panel members. The final content of this statement was agreed on by all panel members and approved by the council of APPS. The current statement covered diagnostic approach, diagnostic criteria, management algorithm, drug-induced sleep endoscopy, medical treatment including medications and positive pressure ventilation, surgical treatment including adenotonsillectomy, orthodontic treatment, and orofacial myofunctional therapy (OMT). Diagnostic criteria of childhood OSAS from 1 year to 18 years were presented that include both clinical (criteria A) and polysomnography findings (criteria B) in the diagnosis of childhood OSAS. The use of nocturnal pulse oximetry as a screening tool was suggested using the McGill oximetry score. Management of OSAS with medical treatment, tonsillectomy and adenoidectomy (TandA), positive airway pressure, orthodontic devices, nasal valves, and OMT were reviewed. Management of persistent OSAS after TandA was addressed, and the importance of weight control was emphasized. The position statement provides a guideline to the management of childhood OSAS in Asia.

Keywords: Child, polysomnography, sleep apnea syndrome, snoring

Introduction

Obstructive sleep apnea syndrome (OSAS) was reported to affect 1%–6% of prepubertal children.[1,2] While standard management guideline has been developed for use in the developed countries in the USA and Europe, management of childhood OSAS in Asia has not been standardized.[1,3,4] The aim of this position statement is to provide guidance to the management of childhood OSAS in Asian children for general pediatricians and general practitioners. To this aim, a group of experts in pediatric OSAS gathered in 2015 during the 1st Annual Scientific Meeting of the Asian Paediatric Pulmonology Society (APPS) held in Hong Kong in October 2015. A panel was formed and was given the task to prepare the position statement based on the current literature, especially that from Asia and the consensus among the group. The group presented the drafted statement in the International Paediatric Sleep Association in Taiwan in March

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2016 and comments were received and the group developed the second draft which was presented in the 2nd Annual Scientific Meeting of APPS in Singapore in November 2016. Further comments were received and revision was done. The final draft was presented to the guideline committee of APPS which recommended the statement to be presented to the executive committee of APPS and approval was granted for the statement to be released as the official position statement of APPS in March 2017.

Definition of Obstructive Sleep Apnea Syndrome

The diagnostic criteria of childhood OSAS are defined in Table 1. The current definition does not cover children younger than 1 year old as infants, especially those younger than 3 months, have different types of breathing disorders during sleep.[5]

Risk Factors for Childhood Obstructive Sleep Apnea Syndrome

Adenotonsillar hypertrophy is the most recognized risk factor of OSAS in children.[6,7] Allergic rhinitis and obesity are other common risk factors.[8-12] Other risk factors include well-known structural abnormalities of the airway, such as micrognathia and midfacial hypoplasia, Down syndrome, Prader–Willi syndrome, achondroplasia, and less well-known and subtle defects such as congenital teeth agenesis and septum deviation, short lingual frenulum, and chronic mouth breathing.[13-18] Neuromuscular disorders such as muscular dystrophies, cerebral palsy, and Chiari malformation are at high risk for OSAS. Other factors include gastroesophageal reflux and premature birth.[19-21] Children with a family history of OSAS are at an increased risk for OSAS. Environmental tobacco smoke exposure was also associated with OSAS.[22,23]

Table 1: Diagnostic criteria of childhood OSAS (1- to 18-year-old)

Criteria A and B must be met
Criteria A: 1 or more of the followings
Habitual snoring, i.e., ≥3 nights per week
Labored breathing (snorting), or observed obstructive apnea during the child's sleep
Daytime sleepiness, hyperactivity, attention deficit, behavioral problems, learning problems, academic deterioration
Hypertension or nocturnal hypertension
Nocturnal enuresis (primary or secondary)
Excessive sweating during sleep
Chronic NREM parasomnias
Criteria B: PSG demonstrates one or both of the following
One or more obstructive apneas, mixed apneas, or hypopneas, per hour of sleep, i.e., AHI ≥1# or
A pattern of obstructive hypoventilation, defined as at least 25% of total sleep time with hypercapnia, i.e., $PaCO_2$ (or validated surrogate marker like $TcCO_2$*) >50 mmHg together with signs of partial obstruction like paradoxical breathing and/or out of phase between chest and abdominal recordings and/or flow limitation

#For children older than 12 years, AHI >5 might be used as the cutoff at the discretion of the attending pediatric respirologist, *$TcCO_2$ should be done with a validated transcutaneous CO_2 monitor with *in vivo* calibration by arterial CO_2 or arterialized capillary CO_2. PSG: Polysomnography, NREM: Non rapid eye movement

Complications of Childhood Obstructive Sleep Apnea Syndrome

Childhood OSAS is associated with neurological and cardiovascular morbidities.[24-29] These neurological morbidities include attention deficit/hyperactivity disorder, hypersomnolence, parasomnia (confusional arousals, sleep terrors, sleep walking, nightmares, and bruxism), depression, aggression, somatization, abnormal social behaviors, and nocturnal enuresis.[30-39] Cardiovascular morbidities include elevated systolic and diastolic blood pressure, dysfunction of autonomic regulation, reduced cerebral blood flow, left ventricular remodeling, and endothelial dysfunction.[25,29,40-46] Childhood OSAS is also associated with growth impairment.[47,48]

Diagnostic Approach

Children of all ages should be screened by their family physicians or pediatricians for the presence of snoring, especially habitual snoring, i.e. 3 or more nights per week and symptoms suggestive of OSAS during routine health checkup [Tables 2 and 3]. If positive, further focused evaluation should be performed.[1]

If there is reported habitual snoring with signs and/or symptoms suggestive of OSAS, further evaluation and management is advised. The approach may vary, depending on the resources available. An algorithm for the evaluation of children with suspected OSAS is suggested in Figure 1.

Sleep polysomnography (PSG), wherever available, is considered the gold standard for diagnosis of OSAS. Attended PSG in the sleep laboratory is preferred, especially for children younger than 4 years old. Several studies demonstrated the validity of unattended study in children but these unattended studies should involve monitoring of electroencephalogram or a way to monitor autonomic nervous system disruption, for example, electrocardiogram + SpO_2 plethysmography.[42,49,50] Nap studies should not be used to substitute these overnight studies.

When PSG, attended or otherwise, is not available, analysis of nocturnal pulse oximetry would provide the second best objective assessment of the child's condition. This monitoring underscores abnormal breathing during sleep as it misses the hypopnea with only arousal. Nocturnal pulse oximetry is a useful diagnostic test only when the OSAS is associated with significant oxygen desaturation. A positive diagnostic test is made when there are 3 or more desaturation clusters (defined as 5 or more desaturations to <90% occurring in a 10–30 min period) [Table 4].[47-49] The positive predictive value and negative predictive value (NPV) of the test were 96.8% and

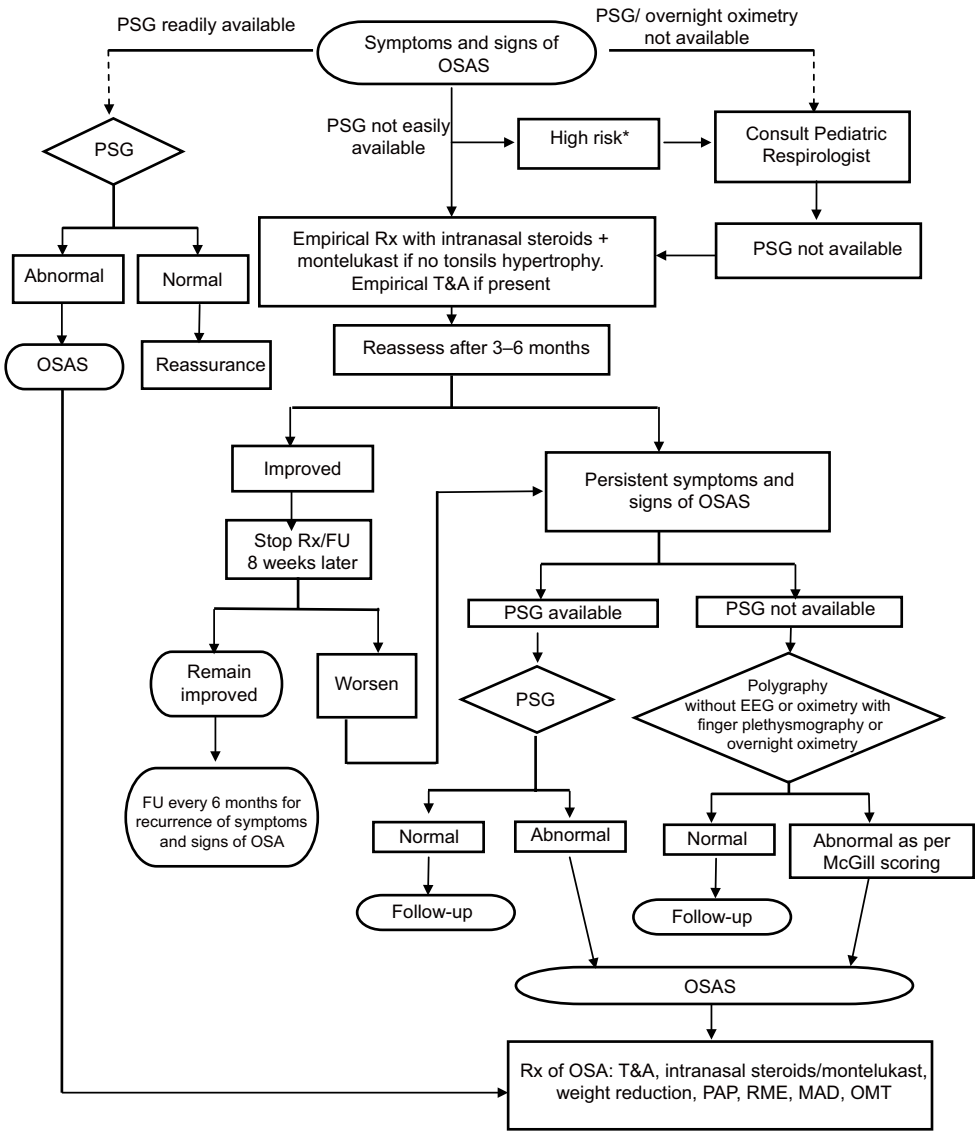

Figure 1: Management algorithm of children with suspected obstructive sleep apnea syndrome. *High-risk group: age <3 years, obesity, chronic mouth breathing, syndromic or nonsyndromic craniofacial growth disorders, chronic gastroesophageal reflux, chronic upper airway allergies, trisomy 21, cerebral palsy, neuromuscular disorders, chronic lung disease, sickle cell disease, genetic/metabolic diseases. Abbreviations: T and A: Tonsillectomy and adenoidectomy; PAP: Positive airway pressure; RME: Rapid maxillary expansion; MAD: Mandibular advancement device; OMT: Orofacial myofunctional therapy.

58.11%, respectively.[51-53] The major limitation of nocturnal pulse oximetry monitoring is the low NPV when OSAS could not be ruled out.

Drug-induced Sleep Endoscopy

Endoscopy has been used to evaluate the upper airway for a long time.[54-56] Good sedation is essential and medications such as midazolam, fentanyl, or propofol are commonly used. As OSAS children are prone to have obstructive apnea/hypopnea with sedation, it is important to have a competent medical practitioner to provide sedation and intervene whenever necessary. Structured reporting format for the findings of endoscopy is important.[57] There are often multilevel obstructions found in patients with sleep-disordered breathing (SDB).[58-62]

Evaluation of four-site "VOTE" was suggested.[63,64] However, this missed out the adenoids in children. Hence, evaluation of six sites was suggested [Figure 2].[65,66]

At the retrolingual level, the degree of hypertrophy of lingual tonsils and features of reflux laryngitis which were commonly associated with obstructive sleep apnea (OSA) should also be noted.[67] Having knowledge of number of sites of obstruction will help to plan management.

Medical Treatment of Childhood Obstructive Sleep Apnea Syndrome

Intranasal corticosteroids

The use of intranasal corticosteroids was shown in a case series by Alexopoulos *et al*. that their use could improve

Table 2: Symptoms of obstructive sleep apnea syndrome

Labored breathing during sleep
Gasps/snorting noises/observed episodes of apnea
Nocturnal enuresis (especially secondary enuresis)
Sleeping in a seated position or with the neck hyperextended
Chronic observed episodic cyanosis during sleep
Headaches on awakening
Daytime sleepiness
Attention-deficit/hyperactivity disorder
Learning problems
Unexplained mood swing
Confusional arousal/sleep walking
Somniloquy

Table 3: Sign of obstructive sleep apnea syndrome

Underweight or overweight
Tonsillar hypertrophy
Adenoidal facies
Micrognathia/retrognathia
High-arched palate
High Mallampati score
Cross or open bite
Increased overjet
Short lingual frenulum
Loud pulmonary component of the second heart sound
Hypertension

PSG findings and OSA symptoms in children with mild SDB.[68]

Later, randomized placebo-controlled trials involving the use of different intranasal corticosteroids, mometasone furoate, budesonide, and fluticasone propionate aqueous spray were shown to decrease apnea-hypopnea index (AHI) [Table 5].[69-71]

A meta-analysis of the above studies conducted by Liu *et al*. in 2016 showed a reduction of AHI by 1.1 with the use of intranasal corticosteroids in children with OSA.[72]

Leukotriene receptor antagonist

Montelukast given for 16 weeks at a dosage of 4 mg/day for <6 years old or 5 mg/day for >6 years old was shown by Goldbart *et al*. in an open-label case–control study involving 46 children aged between 2- and 10-years to be effective in reducing AHI significantly in treatment group, pretreatment 3.0/h to posttreatment 2.0/h, when compared to control group, pretreatment 3.2/h to posttreatment 4.1/h.[73]

Subsequently, Goldbart *et al*. conducted a double–blind, randomized, placebo-controlled trial in children aged between 2- and 10-years that administration of montelukast improved obstructive apnea index (OAI) and AHI significantly.[74]

Kheirandish-Gozal *et al*. published a double-blind, randomized, placebo-controlled trial on the effect of montelukast on OSA children.[75] The study involved 64 OSA children aged between 2- and 10-years and it showed that AHI of treated children

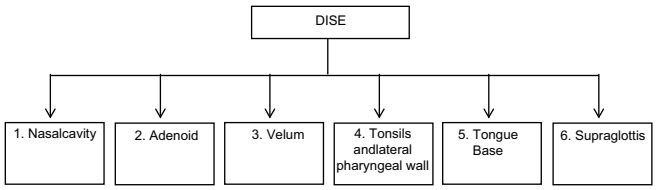

Figure 2: Six important sites recommended for evaluation of obstructive sleep apnea with drug-induced sleep endoscopy.

decreased from 9.2 to 4.2 ($P < 0.0001$) while AHI did not change in those receiving placebo.

A meta-analysis of the above studies was conducted by the authors (DKN, JPN, and SYL) and it showed a reduction of AHI by 2.7 with the use of montelukast [Figure 3].

Combined intranasal corticosteroids and montelukast

Two nonrandomized studies were identified. Kheirandish *et al*. in an open-label control trial (involving 36 children of more than 6 years old) demonstrated that combined use of oral montelukast (4 mg for children <6 years old or 5 mg for children ≥6 years old) and intranasal budesonide (32 mcg/nostril per day) for 12 weeks in postadenotonsillectomy children with residual mild OSA could reduce AHI significantly in treatment group (mean AHI dropped from 3.9 to 0.3) when compared to control group (mean AHI increased from 3.6 to 4.7).[76]

Kheirandish-Gozal *et al*. in a retrospective study showed, involving 836 mild OSA children aged between 2- and 14-years, that the combined use of intranasal corticosteroids and montelukast brought about a significant improvement in AHI.[77]

A meta-analysis of the above studies was conducted by the authors (DKN, JPN, and SYL) and it showed a reduction of AHI by 3.3 with the concurrent use of intranasal corticosteroids and montelukast on OSA children [Figure 4].

Tonsillectomy and Adenoidectomy

Tonsillectomy and adenoidectomy (TandA) is the first-line treatment for children with OSAS with adenotonsillar hypertrophy. The Childhood Adenotonsillectomy Trial (CHAT), a randomized trial of early adenotonsillectomy (eAT) compared to watchful waiting with supportive care (WWSC) for mild-to-moderate childhood OSAS, i.e., AHI ≤5, showed normalization of PSG findings in 79% versus 46% of the respective groups on assessment after 7 months.[78] There were also significantly greater reported reduction in symptoms and improvement in behavior and quality of life in the eAT group than the WWSC group. The significance of the normalization rate of 46% in WWSC group, who nevertheless had worse behavioral performance, warrants further study.[79]

Postoperative complications were reported to be higher in those aged below 3 years, presence of cardiac complications, congenital craniofacial anomalies, neuromuscular disorders, and severe obesity.[80,81] For such high-risk patients, TandA should be performed in facilities with pediatric intensive care

Table 4: The McGill Oximetry Scoring

Score	Comment	Criteria			
		Number of drops in SaO_2 <90%	Number of drops in SaO_2 <85%	Number of drops in SaO_2 <80%	Others
1	Inconclusive for OSA	<3	0	0	Baseline: Stable (<3 clusters of desaturations) and >95%
2	Mild OSA	≥3	≤3	0	3 or more clusters of desaturation events
3	Moderate OSA	≥3	>3	≤3	3 or more clusters of desaturation events
4	Severe OSA	≥3	>3	>3	3 or more clusters of desaturation events

Table 5: Three different intranasal corticosteroids studies in the treatment of obstructive sleep apnea syndrome

Drug	Sample size	Age (year)	Regimen
Mometasone furoate[69]	62	6-18	100 μg/nostril daily for 4 months
Budesonide[70]	62	2-12	32 μg/nostril daily for 6 weeks
Fluticasone propionate[71]	25	1-10	50 μg/nostril twice per day for 1 week, followed by 50 μg/nostril daily for 5 week

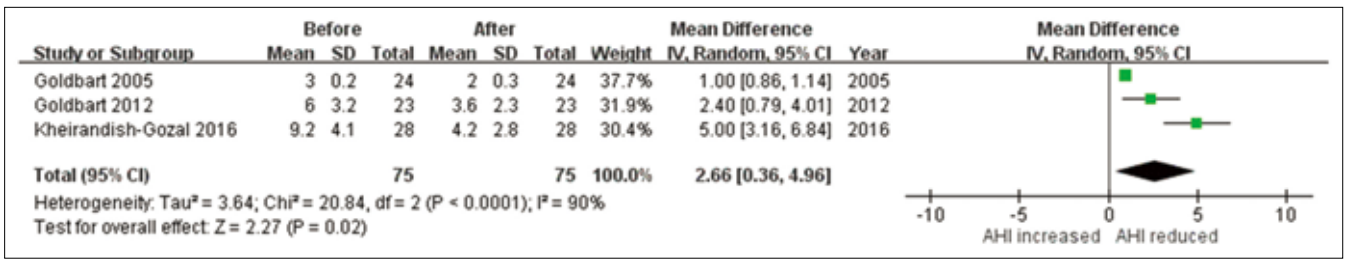

Figure 3: Forest plot for the effects of montelukast on apnea–hypopnea index.

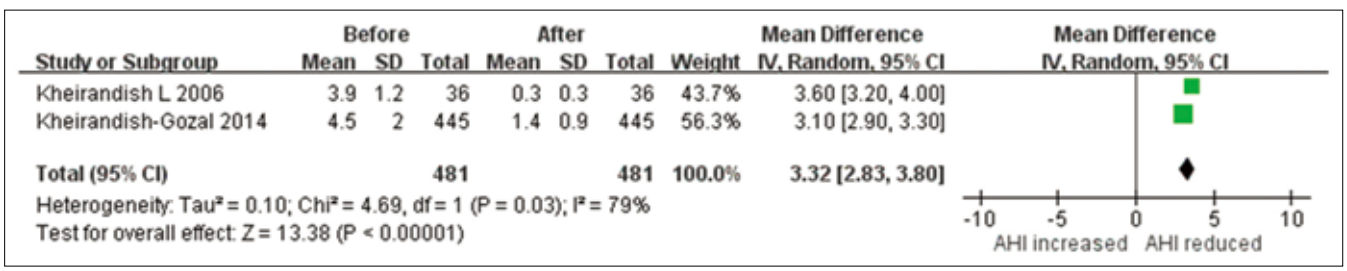

Figure 4: Forest plot for the effects of montelukast combined with intranasal steroids on apnea–hypopnea index.

service. Furthermore, a delay in performing TandA should be considered for patients with recent respiratory infections.

Reevaluation with PSG several months after TandA is recommended to evaluate for residual OSAS. There were no studies evaluating the timing of postoperative PSG evaluation. The recommendation of a few months is to allow healing and resolution of inflammation and swelling of the operative site before reassessment.[80,82-84] If PSG is not available, other options outlined in the "management algorithm of OSAS" may be considered.

The prevalence of residual OSAS after TandA ranged from 34% to 87% in the literature, depending on the characteristics of the study population and AHI definition used for residual OSAS.[85] A meta-analysis of the effect of TandA on AHI was undertaken by the authors (DKN, JPN, and SYL). Databases including PubMed, MEDLINE, EMBASE, and Cochrane Review from 1998 to 2015 were searched. The keywords used included tonsillectomy, adenoidectomy, OSA, sleep apnea, sleep apnea syndrome, and children. Success as defined by postoperative AHI <5 for all children and obese children was 80% and 55%, respectively [Figures 5 and 6], and it decreased to 55% and 30%, respectively, if success was defined as AHI <1–2 [Figures 7 and 8].[79,80,82-84,86-117]

The risk factors for residual OSAS after TandA are severe OSA at baseline, asthma, obesity, or weight gain after TandA, trisomy 21, cerebral palsy, craniofacial abnormalities, upper/lower airway abnormalities, for example, laryngomalacia.[86,93-96,100,105,107,110,114,118-120]

Growth data from the CHAT showed that TandA for OSAS in children resulted in significantly greater than expected weight

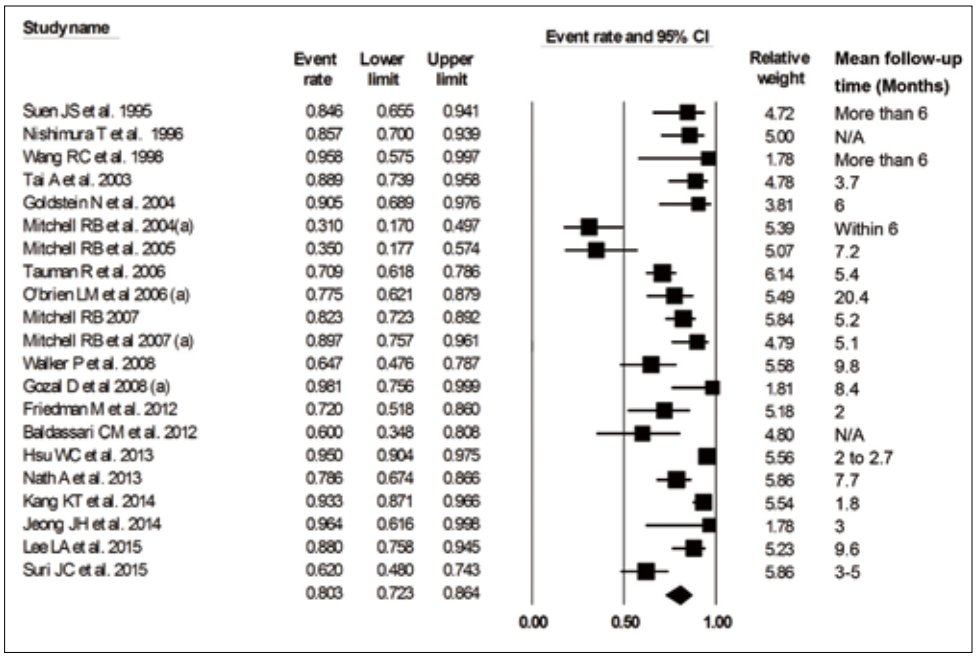

Figure 5: Forest plot for success in achieving an apnea–hypopnea index <5 postoperatively in children (not classified by body mass index). There was significant heterogeneity among these studies ($I^2 = 82.53$). Data were analyzed with random-effects model estimate.

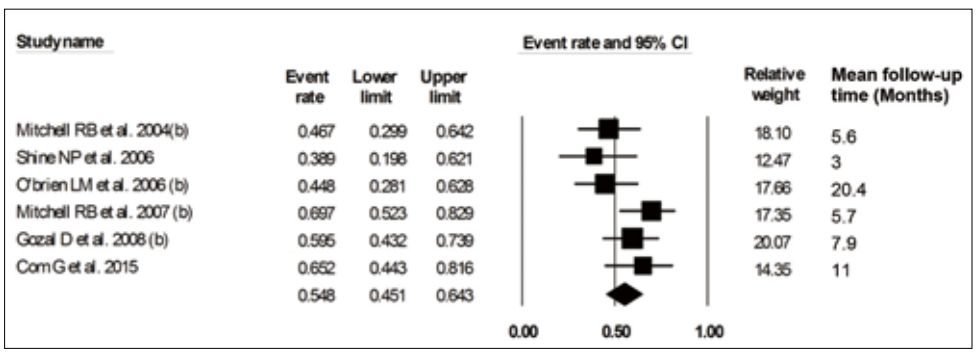

Figure 6: Forest plot for success in achieving an apnea–hypopnea index <5 postoperatively in obese children. There was significant heterogeneity among these studies ($I^2 = 36.62$). Data were analyzed with random-effects model estimate. Obese was defined as Z-score from >1.2, ≥2 to ≥2.33 or body mass index ≥95th percentile.

gain from baseline, even in initially overweight children.[121] This puts overweight children at greater risk of residual or recurrent OSAS after TandA.[120]

The management of residual OSAS after TandA is dependent on the severity of the residual OSAS. Further diagnostic tests (e.g., drug-induced sleep endoscopy [DISE], cine magnetic resonance imaging) to evaluate the level of obstruction may be useful.[63,117,119,121]

Huang *et al*. demonstrated that 53% of children had an AHI >1 at 6-month follow-up after TandA, it increased to 68% at the end of the 36-month follow-up. Risk factors for recurrence of OSAS such as severe OSAS, obesity, and a large increase in body mass index after TandA, allergic rhinitis, enuresis, and older age were identified.[115] Biggs *et al*. performed a 4-year follow-up study for school-aged children (12–16 years old). Improvement in SDB was associated with improvements in some aspects of neurocognition but not behavior among the children. Therefore, it was suggested that a longer period of follow-up was required to observe the neurocognitive changes.[122] The treatment options for persistent or recurrent OSAS after TandA are listed in Table 6.

Orthodontic Treatment

Orthodontic treatment (e.g., rapid maxillary expansion [RME], mandibular advancement devices [MAD]) may be an effective treatment option for childhood OSAS in a selected group of patients. There are, however, limited studies on orthodontic treatment for pediatric OSA, with the majority of studies being nonrandomized clinical trials.

RME is an orthodontic treatment which increases the transverse diameter of the hard palate by reopening the mid-palatal suture with an expandable dental appliance inserted into the

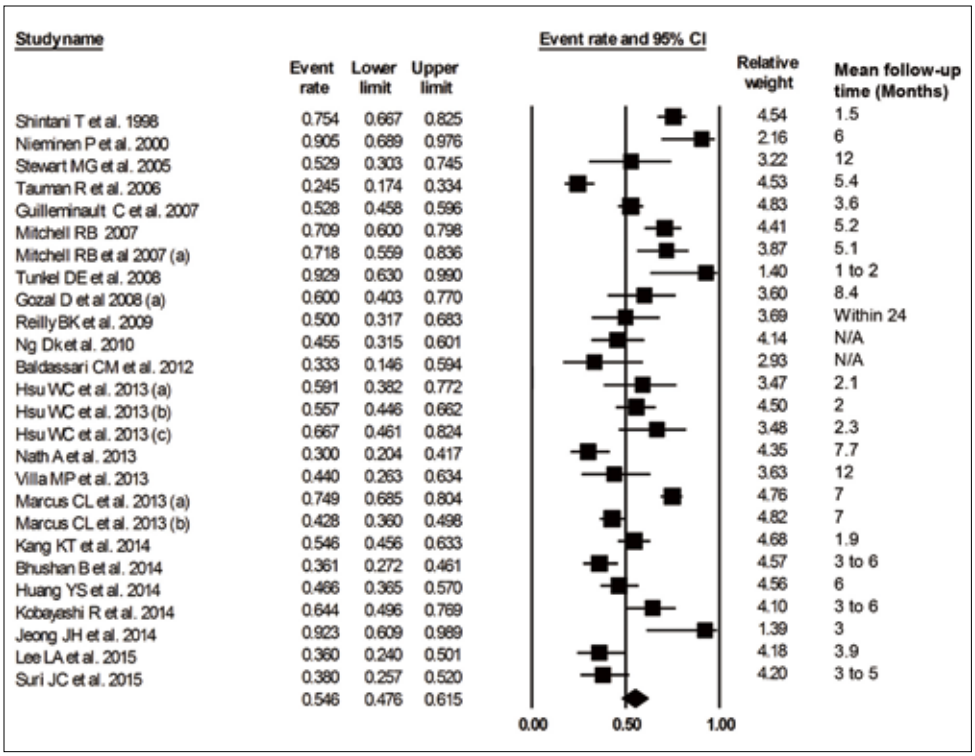

Figure 7: Forest plot for success in achieving an apnea–hypopnea index <1–2 postoperatively in normal children (those have not been classified by body mass index). There was significant heterogeneity among these studies ($I^2 = 85.77$). Data were analyzed with random-effects model estimate.

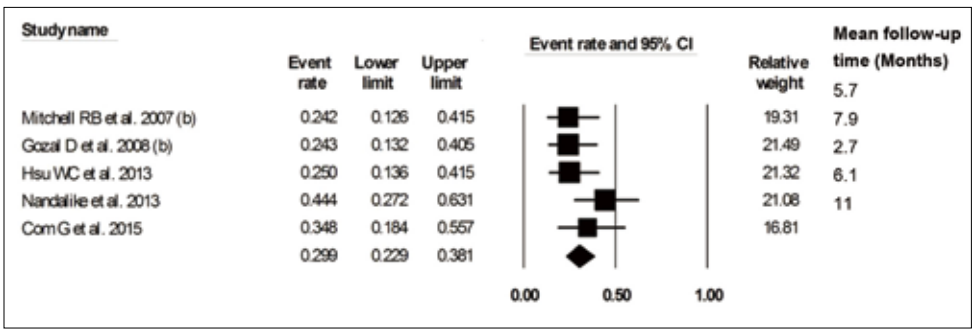

Figure 8: Forest plot for success in achieving an apnea–hypopnea index <1–2 postoperatively in obese children. There was significant heterogeneity among these studies ($I^2 = 8.11$). Data were analyzed with random-effects model estimate. Obese was defined as Z-score from 1.2 to ≥2.33 or body mass index ≥95th percentile.

mouth close to the hard palate. It also has a secondary impact on placement of the mandible. It may be an option in the management of OSA in children with maxillary contraction, with long-term treatment effect shown in follow-up studies.[113,124-128] A meta-analysis of RME was undertaken by Huynh *et al*. who reported that the AHI decreased by 6.2 after using RME from four studies.[129]

MADs increase the upper airway size by positioning the mandible and tongue forward.[130] In the same review by Huynh *et al*., a meta-analysis of MADs on two studies was undertaken.[129,131,132] With MAD, the AHI decreased by 5.1.

The authors (DKN, JPN, and SYL) updated the meta-analysis by searching databases including PubMed, MEDLINE, EMBASE, and Cochrane Review from 2001 to 2015. The keywords used included sleep apnea, OSA, sleep apnea syndrome, MAD, and children. RevMan (version 5.2, The Cochrane Collaborations, London, UK) was used for the meta-analysis. AHI was found to be decreased by 6.5 with MAD treatment [Figure 9] from three studies.[131-133]

Nasal Expiratory Positive Airway Pressure Valve

This device comprises two small adhesive disposable valves applied to both nares. The valves have negligible resistance during inspiration, but generate resistance during expiration, creating a positive end-expiratory pressure from 4 to 17 cmH_2O.[134] Initial studies showed reduction in AHI and symptoms in adults with OSA, but subsequent studies did

Table 6: Treatment options for persistent obstructive sleep apnea syndrome after tonsillectomy and adenoidectomy

Treatments	Comments
Watchful waiting	Generally for mild OSAS, AHI <5, with few or no symptoms and no complications of OSAS
Medical treatment	Nasal corticosteroids and/or leukotriene receptor antagonist[76]
Weight loss	Weight loss is a treatment option for OSAS in overweight/obese children[123]
Positive airway pressure	For moderate/severe OSAS, AHI ≥5
Orthodontic treatment	For mild-to-moderate OSAS
Orofacial myofunctional therapy	For mild-to-moderate OSAS
Other surgical options	Other surgical procedures are considered in a small subset of children with OSAS, after careful evaluation of the upper airway in children with moderate/severe OSAS. Options include tongue surgery, for example, midline glossectomy, genioglossus advancement, maxillo and/or mandibular distraction osteogenesis or tracheostomy[98,113]

OSAS: Obstructive sleep apnea syndrome, AHI: Apnea-hypopnea index

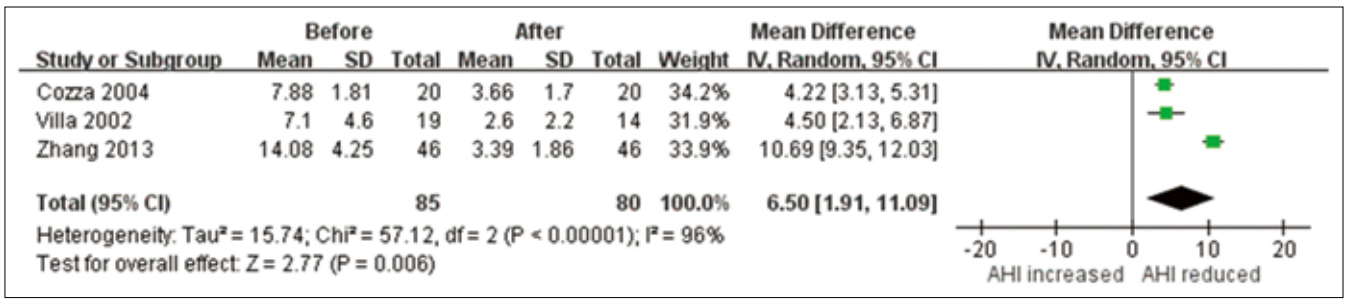

Figure 9: Forest plot for the effects of mandibular advancement device on apnea–hypopnea index.

not show benefit in adults with moderate-to-severe OSA.[135,136] A recent randomized, double-blind, placebo-controlled, crossover pilot study of nasal expiratory positive airway pressure (NEPAP) device on 14 CPAP candidates aged 8–16 years showed significant improvement in OAI with NEPAP in some patients but deterioration in a few patients, suggesting that it must only be prescribed under PSG monitoring.[137]

Positive Airway Pressure

The basic mechanism of positive airway pressure (PAP) is to overcome dynamic upper airway obstruction by stenting the airway open by pneumatic pressure. PAP therapy has been found to be effective in improving polysomnographic parameters in pediatric patients with OSAS.[138-143] In addition, there were also improvements in subjective parental assessment of sleepiness, snoring, and difficulty in breathing during sleep.[138] Significant improvement in neurobehavioral function in children after 3 months of PAP therapy was demonstrated, even in developmentally delayed children.[142]

PAP therapy should be considered in children who are not surgical candidates or have contraindications for TandA and those who continue to have moderate/severe OSAS after TandA.[143-145] PAP may also be considered for children with severe preoperative OSAS, co-existing morbidities such as cor pulmonale, morbid obesity, neuromuscular disorders, and craniofacial abnormalities.[87,96]

There are two modes of PAP – continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP). There is no difference in adherence between CPAP and BPAP.[146] The optimal setting should ideally be adjusted under PSG.[147] The maximum CPAP is 15 cmH_2O for <12-year-old children and 20 cmH_2O for ≥12-year-old children. CPAP should be switched to BPAP if the patient demonstrates persistence of OSA despite maximum CPAP. For BPAP, the inspiratory positive airway pressure should be started at 4 cm above the expiratory positive airway pressure (EPAP), and the EPAP pressure set at the level eliminates OSA. Long-term follow-up is needed since the required PAP setting may change over time for growing children with change in airway size and structure, as well as body weight.

If PSG titration is not available, the use of auto-titrating PAP devices for titrating pressures can be considered in patients down to 8 months of age without significant comorbidities although the body weight for auto-titrating PAP is usually above 30 kg.[148] PAP also can be titrated under DISE in selected centers with expertise.

In areas where none of the above are available, one may offer CPAP with pressure around 6–8 cmH2O for nonobese nonsyndromic OSAS and 8–10 cm for obese nonsyndromic children and to monitor for clinical response.[139] Data downloaded from PAP machines are useful in monitoring treatment adherence as parental reports are often not reliable.[146]

Adherence is the major barrier to PAP as an effective therapy for childhood OSAS.[146,149,150] Behavioral intervention, education, training, and close follow-up were shown to improve PAP adherence.[151]

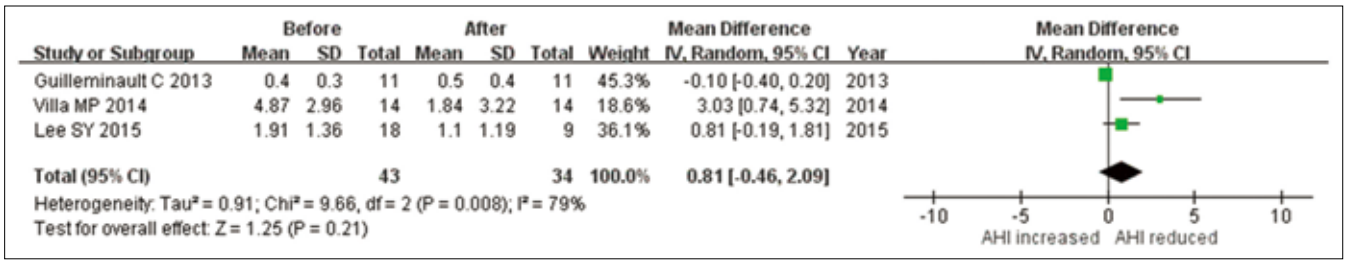

Figure 10: Forest plot for the effects of myofunctional therapy on apnea–hypopnea index.

A proper interface is crucial for the successful administration of PAP. The ideal interface should ensure comfort and fit, while minimizing leak.[152] Excessive leak can impact on sleep quality, patient–ventilator synchrony, and the amount of effective ventilation delivered to the patient.[153] If a child mouth breathes significantly, a chin strap should be used.

PAP should be provided with a heated humidifier because of the high flow of dry room air that would overwhelm the capacity of the nose to humidify and warm the incoming air. Notwithstanding the above measure, some patients would still have prominent nasal symptoms that would benefit from intranasal steroids. Skin irritation and ulceration can occur from a tight-fitting mask or from accumulation of skin oils and debris from poor mask maintenance.[154-157] Mid-facial hypoplasia was reported with long-term use of nasal CPAP.[158] A study showed that nasal PAP compliant individuals experienced a retrusion of the mid-face after a few years.[159] Use of nasal mask and nasal pillow on alternate nights might be tried to avoid the pressure effect on mid-face. Facial profile should be assessed every year for adverse impact on growth. For children requiring chin strap, the effect on the mandibular condyle should also be assessed yearly.

Orofacial Myofunctional Therapy

Orofacial myofunctional therapy (OMT) is potentially an option for the treatment of OSAS. It is defined as the treatment for the muscles of the face and mouth, which is crucial for the maintenance of the craniofacial integrity to achieve normal nasal breathing.[160] OMT reeducation trains a normal and strong sucking, a good mastication employing both sides of jaw, normal swallowing, normal tongue position, and nasal breathing with lips in good contact at rest.[13] Nasal breathing during wake and sleep is the demonstration of normal respiratory functioning, and persistence of mouth breathing is an indicator of an abnormal respiratory function.[161]

Guilleminault *et al*. reported a retrospective study of 11 children who received OMT.[162] The exercise group was followed up for the first 6 months. Exercise was repeated several times daily in the first 6 months. At 4-year follow-up, the exercise group remained cured of OSA (AHI 0.5 ± 0.4/h) compared to the control group which had a recurrence of OSA (AHI 5.3 ± 1.5/h).

In a prospective, randomized controlled study done by Villa *et al*., 27 post-TandA children were randomized to either OMT or control group.[163] Children were required to perform exercises every day at home, at least three times a day, 10–20 repetitions each time. Both groups performed nasal washing twice a day. The treatment group consisted of 14 patients and their pre- and post-exercise AHI was evaluated after 2 months of OMT. The AHI decreased from 4.9 to 1.8 ($P = 0.004$) while the control group had minimal change in AHI (4.6–4.1).

In a retrospective case series study done by Lee *et al*., 26 children out of 64 children had persistent SDB after TandA and 35 of the 64 children showed a pattern of mouth breathing.[161] Eighteen children of the mouth breathing group were followed up for a year with OMT offered. However, only nine of them underwent 6 months of OMT three times a week. The non-OMT group showed a significant worse AHI, 2.9, when compared to the exercise group, 1.1.

A forest plot was constructed with RevMan (version 5.2, The Cochrane Collaborations, London, UK) for the studies of Villa *et al*., Guilleminault *et al*., and Lee *et al*. by the authors (DKN, JPN, and SYL, respectively). The overall AHI was reduced by 0.81 with 95% confidence interval crossing zero [Figure 10]. Hence, further studies are warranted for OMT in childhood OSAS.

Conclusion

This is the first position statement on the management of childhood OSA in Asia, which would serve as a guideline for doctors in this area so that a more uniform approach can be adopted for this disease. While there are still considerable knowledge gap in this area, this statement provides the foundation for future studies.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Pediatric Obstructive Sleep Apnea: A Short Review of Clinical Aspects

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Abstract

This report reviews the historical developments leading to recognition of pediatric obstructive sleep apnea. It briefly summarized the rationale why the upper airway becomes at risk of collapsibility during sleep. It also reviews the complaints that vary with age. It emphasizes points of the examination that must be systematically look for. The report reviews the variables to monitor, to look for, and to be analyzed, and patterns not often looked at but that disturb sleep and lead to complaints and symptoms in sleep polysomnography.

Keywords: Clinical evaluation, complaints, flow limitation, obstructive sleep apnea, pediatrics, polysomnography

Introduction

Sleep-disordered breathing (SDB) involved a decrease in the lumen of the upper airway (UA) during sleep. Historically, this decrease was noted to occur a variable degree overtime, based on the instrument used to investigate this decrease. Initially, respiration during sleep in children was monitored during sleep using nasal and oral prongs or thermistors, thoracic and abdominal strain gauge, calibrated esophageal pressure (Pes), Water™ ear oximeter, finger plethysmography, thoraco-diaphragmatic electromyography (Dia-EMG), and a neck "microphone" that did not measure decibel but power of UA sounds. In specific research cases, a tightly placed facial mask with a pneumotachograph was used, allowing measurements of tidal volume, expired CO_2, proper timing of inspiration time (Ti) expiration time (Te), and variable degree of airflow limitation with or without arterial line placed that allowed continuous monitoring of blood pressure and to intermittently draw arterial blood for blood gases measurements. These respiratory parameters were those used historically for the description of sleep apnea in children. The monitoring of Pes allowed one to accurately describe when there was a decrease in respiratory effort or an increase of such effort. The "dia"-EMG gave a similar indication but was not exactly quantifiable. The nonresearch montage used on all children seen at the Stanford University Sleep-disordered Clinic allows diagnosis of children "apnea"-complete cessation of air exchange at nose and mouth and hypopnea, a partial cessation of air, exchange at nose and mouth. The oximeter indicates a drop of oxygen saturation. The Pes indicated if there was an increase or decrease in effort in association of the abnormal breathing pattern, and based on the recording, an "obstructive" or "diaphragmatic" (called by others "central") was scored. Simultaneously, sleep/wake markers 3 (electroencephalography [EEG] leads), chin muscle EMG, eye movements (2 leads), and one electrocardiographic leads were monitored, allowing recognition of sleep stages and wakefulness and also changes in autonomic nervous system (ANS) activity using plethysmography and heart rate recordings. These recordings led to the report of "obstructive sleep apnea (OSA) in children" and in infants.[1-3] The usage of the full face mask with pneumotachograph and Pes indicated that abnormal breathing during sleep was not limited to the above patterns and that there was in some children presence of a limitation of airway flow with increase in effort without evidence of drop in oxygen saturation. This was called "obstructive breathing," and it was reported to be seen frequently with snoring and disturbance of the sleep EEG.[4] When the pattern was verified by many, the term "Respiratory

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Related Respiratory Arousal (respiratory event related arousal [RERA])" was applied in the mid-1990s.[5] By that time, efforts were made to replace the thermistors/thermocouples that measured change in temperature but not change in flow by more sophisticated equipment. The laboratory of Rapoport in New York was very much involved in this development. Hosselet *et al*. in 1998 demonstrated that a nasal cannula/pressure transducer system[6,7] could provide a noninvasive indicator of flow limitation that can identify periods of elevated UA resistance both in normal participants and those with SDB, and the equipment was recommended as the valid standard for monitoring of nasal breathing in 2000. "Flow Limitation" was calculated as a percentage of total sleep time. Instead of recording nasal cannula, some authors monitored end-tidal CO_2 or tried to monitor both signals after 1992, but such double recording was shown to be difficult. With the improvement of transcutaneous CO_2 ($TcCO_2$) monitoring, such recording has been common after 2000.

Duration of events monitored during sleep was adjusted to age; abnormal obstructive breathing was scored if events lasted longer than two breaths (i.e., 3 breaths); in neonates, such duration was 3 s, at 12 months 6 s, and older age 10 s.[3]

Most of the descriptions of abnormal breathing are back to these historical descriptions. If Pes is uncommonly monitored today, noninvasive nasal cannula pressure transducer is the norm as it is $TcCO_2$ monitoring. Such montage has eliminated the possibility to score "central hypopnea" as "effort" cannot be monitored with nasal cannula but only with Pes.

The Upper Airway and Sleep

The pharynx is a collapsible tube, unlike lower airways, it has no rigid support, and the skeletal muscles and soft tissues support nonrespiratory functions: sucking, swallowing, vocalization/phonation, etc. However, the physiology during wakefulness is different from sleep; sleep causes fundamental modifications of pharyngeal muscle tone and reflex responses and can lead to narrowing and increased UA resistance in normal individuals. Muscle tone decreases during sleep and its decrease will be different during nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep when it will be more significant. Also there is a greater risk of UA increased resistance at end inspiration during sleep: During wakefulness the decrease in lung inflation and decrease in lower airway size, normally induce a reflex that increases the tonic activation of the UA muscles, but this reflex is decrease during NREM sleep and is inactive during REM sleep.

The UA can be modelled using fluid dynamics physics, Experimentally, normal participants treated with subatmospheric nasal pressure develop OSA. Each individual has a critical pressure (Pcrit) or intrinsic collapsibility and a level of pharyngeal muscle activity that stiffens and enlarges the airway.[8,9] Experimentally normal participants treated with subatmospheric pressure develop OSA at a variable point: Some subjects have a Pcrit at an atmospheric pressure level and will have a greater of UA collapse if the pressure during expiration goes below their Pcrit as subatmospheric pressure will develop during this phase of the respiratory cycle. Moreover, normally subatmospheric pressure in the UA causes reflex activation of nose and palate dilators (alai nasi, palatoglossus, levator/tensor palatini), oral pharynx/hyoid (genioglossus, geniohyoid, sternohyoid, sternothyroid), and larynx (cricoarytenoid and cricothyroid) – both tonic and respiratory cycled, but this reflex decreases and disappears during sleep, maximum during REM sleep but marked during NREM sleep.

Different factors may play a role in increasing the risk of collapsibility during sleep. Some of these factors involve the neuromuscular control of the UA and the complicated reflex loops involved in this control, and we are lacking information on this aspect particularly during sleep.

There are factors that are "nonsleep" related and that have been studied in the recent time, they are "external factors" that impact on the size of UA, particularly when located retropalatal and retroglossal. These external factors can be influenced by genetic and environmental factors and four factors have been identified: (a) bone structures (oral-facial bones), (b) infiltration of soft tissues - major factor being fat and fat at infiltration of UA is associated with central obesity leading to chest bellows impairment and complex respiratory-ventilatory problem, (c) leukotriene, and (d) inflammation arising from abnormal breathing during sleep.

Summary of Clinical Evaluation

During clinic visits, children must have a pediatric evaluation including body mass index (BMI), vital signs, and neck circumference measurements.[10] The pediatric sleep questionnaire[11] is commonly used.

Complaints will vary with age as follows:

Infants

Disturbed nocturnal sleep with repetitive crying, poorly established day/night cycle, noisy breathing or snoring, nocturnal sweating, poor suck, absence of normal growth pattern, or failure to thrive, observation of apneic events, report of apparent life-threatening event, and presence of repetitive earaches or upper respiratory infection (URI).

Toddlers

Noisy breathing or snoring, agitated sleep or disrupted nocturnal sleep, crying spells or sleep terrors, grouchy and/or aggressive daytime behavior, daytime fatigue, nocturnal sweating, mouth breathing, poor eating or failure to thrive, repetitive URI, and witnessed apneic episodes.

Preschool children

Regular, heavy snoring, mouth breathing, drooling during sleep, agitated sleep, nocturnal awakenings, confusional arousals, sleepwalking, sleep terrors, nocturnal sweating, abnormal sleeping positions, and persistence of bedwetting;

abnormal daytime behavior and aggressiveness; hyperactivity; inattention, daytime fatigue, and hard to wake up in the morning; and morning headache, increased need for napping, compared with peers, poor eating, growth problems, and frequent URI.

School children

Regular, heavy snoring; agitated sleep; abnormal sleeping positions; insomnia; delayed sleep phase syndrome; confusional arousal; sleepwalking; sleep talking; persistence of bedwetting; nocturnal sweating; hard to wake up in the morning; mouth breathing; drooling; morning headache; daytime fatigue; daytime sleepiness with regular napping; abnormal daytime behaviors/pattern of attention-deficit/hyperactivity disorder; aggressiveness; abnormal shyness, withdrawn and depressive presentation; learning difficulties; abnormal growth patterns; delayed puberty; repetitive URI; and dental problems such as a crossbite, malocclusion (Class II or III), and small jaw with overcrowding.

Evaluation

The suspicion of SDB indicates the need not only for a general pediatric evaluation but also for a thorough evaluation of the UA anatomy.

Starting with the nose, one should look for asymmetry of the nares, a large septal base, collapse of the nasal valves during inspiration, presence of a deviated septum, or enlargement of the inferior nasal turbinates.

Next, the oropharynx should be examined for the position of the uvula in relation to the tongue. Presence of a short lingual frenulum using Kotlow measurement and Queiroz Marchesan scale,[12,13] much more common than a short nasal frenulum.[14] The scale developed by Mallampati *et al*. reviewed by Friedman *et al*.[15] may help evaluating the narrowness of the upper airway. There should be systematic search for missing teeth questioning subject and parents and requesting if necessary help of pediatric dentist with performance of specific X-rays (Panorex).[16] The size of the tonsils should be compared with the size of the airway; application of a standardized scale is useful.[17] The presence of a high and narrow hard palate, overlapping incisors, a crossbite, and an important (>2 mm) overjet (the horizontal distance between the upper and lower teeth) are indicative of a small jaw and/or abnormal maxillomandibular development.[18]

This clinical evaluation provides important details of the UA anatomy and identifies anatomical risk factors that can predispose one to the development of abnormal breathing. The results of this examination must be summarized as the different anatomical narrowings have additive effects. The apparent sizes of tonsils and adenoids are not the only anatomical findings that determine whether or not SDB is present. A change in flow due to an abnormal nose, secondary development of turbulence, and the increased collapsibility at specific vulnerable points in the UA are elements to consider.

Recording Sleep-disordered Breathing

Testing during sleep is the only way to confirm the presence of SDB. Controversy exists concerning the need for and type of test to be performed. Polysomnography (PSG) is described above, and its results are considered as the most accurate. Home study will have less reliability than laboratory studies, but if performed, home studies should have sleep/wake monitoring.

Compared to PSG, nocturnal polygraphy has been performed; it usually involves monitoring of a limited number of the respiratory leads, particularly nasal cannula and oxygen saturation; usually an EEG lead is also monitored. This monitoring device can confirm the presence of abnormal breathing during sleep, but if study is negative, the study cannot affirm the absence of breathing problem during sleep.

An increase in respiratory efforts is associated with changes in ANS settings as measured by nocturnal polygraphic arterial tonometry or pulse transit time (PTT).

These changes will affect the cardiovascular system: In an individual with normal autonomic-nervous-system –ANS-, two types of responses can be seen when an increase in respiratory effort occurs during sleep: activation or arousal with cortical involvement. Activation is related to the recruitment of sensory inputs that will lead to a polysynaptic motor response after relay of sensory input in the brainstem and subcortical structures. An ANS response may be seen with brainstem reflexes leading to full reopening of the UA without EEG cortical arousal, or it may be seen as the consequence of an EEG cortical arousal.

The presence of cortical arousals will be associated with clinical symptoms such as complaints of excessive daytime somnolence, irritability, or unrefreshing sleep. The role of repetitive "activation" is unknown in children. Some ambulatory equipment's recognition of SDB is based on ANS responses, using algorithms, commonly associating results of heart rate, and finger plethysmography analyses. The algorithms are proprietary and undisclosed. Such equipment identifies nocturnal sleep disruption, together with monitoring of oxygen saturation and has been considered to provide information equivalent to those obtained with the limited home recordings.

Recording of variables such as pulse-transit-time-PTT-provided by a device using changes in ANS, cannot be used to recognize abnormal breathing during sleep, but recording of "PTT" may be performed in association with other variables during sleep. As a research tool, it has been used in association with PSG to indicate changes in ANS status with identification of sympathetic activation.

Nocturnal oximetry

This is the simplest type of continuous recording. It does not recognize sleep and wakefulness but may indicate the validity of treatment, particularly positive airway pressure or evidence of abnormal repetitive hypoxemic events during the nocturnal period.

Continuous transcutaneous CO_2 monitoring

For a long time, long-term $TcCO_2$ monitoring was considered unreliable, this is not true anymore, but need for change in placement of electrode, need for calibration, and recalibration if sensor is moved are the limitations. This recording may be more helpful in some specific conditions, particularly in children with hypoventilation during sleep related to any cause. If it is not a diagnostic tool in isolation, it may be helpful to follow treated patient at home.

Scoring polysomnography

By 12 months of age, sleep EEG is well developed, and scoring sleep using the Rechtschaffen and Kales criteria and the AASM criteria for short arousal are easy.[19-21]

Furthermore, respiratory rate (RR) is relatively steady from 2 years on between 16 and 18 breaths/min for Stages 2–4 of NREM sleep 17 and 19 breaths/min during REM sleep.

Defining a respiratory event

Event begins at the start of inspiration of the first abnormal breath. If the start of the inspiration is not detectable (such as incomplete apnea or central apnea), the respiratory event will start at the end of expiration of the last detected breath before the abnormal respiratory event. It ends at the start of inspiration of the breath following the abnormal respiratory event.

Definition used

Apnea[20] is more than 90% fall in airflow at the nose and mouth for longer than 2 breaths, independent of oxygen desaturation, change in EEG, or stages of sleep. It is subdivided in central, mixed and obstructive based on airflow and inspiratory efforts.

Hypopnea

An hypopnea[20,21] is a breathing event lasting at least longer than 2 breaths (i.e., 3 breaths) independent of age of the child (1–18 years). It is scored based on nasal cannula pressure transducer (scoring without esophageal manometry); it is associated with a decrease of the curve by 30% compared to the 3 min prior baseline recording. An hypopnea begins with the drop of the nasal cannula curve to reach a 30% drop during one breath. The hypopneas end when the nasal cannula returns to baseline. The duration of the hypopneas is calculated from the inspiratory movement of the first abnormal breath till the inspiratory movement of the first normal breath.

Stanford adjustment rule

This first breath associated with the arousal may show indication of increased movement amplitude above prior baseline volume and associated with short-lived hyperventilation. If there is more than 1 breath during the arousal period (i.e., at least two successive breaths are required to perform a comparison), the drop in amplitude preceding the arousal may be calculated compared to the breaths associated with the arousal.[22]

Investigation of other respiratory signals should be performed for the breaths involved in the hypopneas: (1) checking presence/absence of increase in inspiratory muscle EMG simultaneously with movement and change in amplitude of the inductive thoracic and/or abdominal belts; such association indicates the presence of obstructive hypopneas. If there is a decrease in all of the above signals during hypopneas, "central hypopneas" as seen in association with phasic events of REM sleep may be suspected but cannot be affirmed without Pes recording.

Obstructive hypopnea

The definition is based on nasal pressure transducer; discernable reduction in the baseline signal amplitude for >2 breaths (3 or more breaths) with persistent respiratory effort associated with an EEG arousal or with oxygen desaturation.

The EEG pattern can be associated with a change of the plethysmographic curve with a visually recognizable descending and short-lived curve pattern indicative of a sympathetic activation. Sympathetic activation cannot *per se* indicate EEG arousal as "sympathetic activation," i.e., stimulation at brainstem but stopped by thalamic gate may occur. However, "sympathetic activation may help recognizing EEG arousals."

Hypopnea with usage of esophageal pressure

Pes makes recognition of hypopnea and other abnormal breathing patterns easier. Pes helps in recognition of hypopnea onset with a change in Pes amplitude compared to prior recorded breaths and allows quantifying (after Pes calibration) the amount of change in inspiratory effort associated with each breath. Patterns such as "Pes crescendos," "sustain continuous effort," and "Pes reversal" are systematically looked for. (a) Pes crescendo: sequence of four or more breaths that show increasingly negative peak end inspiratory pressure seen with Pes. (b) Continuous sustained respiratory effort: Definition: repetitive, abnormally negative peak end-inspiratory Pes ending at the same negative inspiratory pressure without a crescendo pattern. It is associated with continuous airflow limitation on nasal cannula pressure transducer signal. Pes allows defining hypopneas with a decreased effort (such as seen in REM sleep).[23-25]

Other Patterns of Abnormal Breathing

Flow limitation

Evaluation with nasal cannula pressure transducer allows recognition of flow limitation. Definition: flattening of the peak of the nasal cannula pressure transducer wave contour, **or** change in the normal round presentation of the peak of the nasal cannula. It is very often but not always associated with changes in Pes recording (and a change in Pes may not be associated with a pattern of flow limitation). It is also often associated with snoring. It may involve one or several breaths. It is not associated with a 3% or 4% SaO_2 drop. The "time spent in flow limitation" is the calculated variable. At least four successive breaths must be associated with abnormal wave contour. The

duration of flow limitation is calculated from the time of the start of flattening to the time when the wave contour normalizes or returns to baseline. The report indicates the total time of flow limitation from total sleep time and the longest episode of flow limitation (in minute and second).[26,27] Systematic usage of Pes indicates that flow limitation is associated with systematic increase in inspiratory effort. Flow limitation is associated with abrupt EEG changes that have been described using a different EEG scoring system called the "cyclic alternating pattern" (CAP) scoring system [Figure 1].[28]

Respiratory event-related arousals

Historically, it was defined before flow limitation, and it was related initially to snoring sound and EEG arousal. It is a sequence of breaths ≥10 s characterized by increasing respiratory effort or flattening of the nasal pressure waveform it terminates with an arousal from sleep, and the sequence does not meet criteria for AASM apnea or hypopnea. The major difference with definition of "flow limitation" is that RERAs count only one event at the end of flow limitation period that ends with a 3 s EEG arousal. Studies of "flow limitation"[26,27] have shown that if "arousal" is scored with a different definition, there are more sleep disturbances - the cause of complaints, signs, and comorbidities - than when just RERAs are scored. However, usage of the CAP[28] that scored an EEG arousal with much shorter EEG changes (i.e., phase A2 of CAP system), or usage of fast Fourier Transform to analyze EEG with a 1 s window have shown that there were more sleep disturbances than when scoring "arousal EEG" lasting 3 s while the cortex react in 300 milliseconds; "flow limitation" may be a better approach but more normative data are needed [Figure 2].

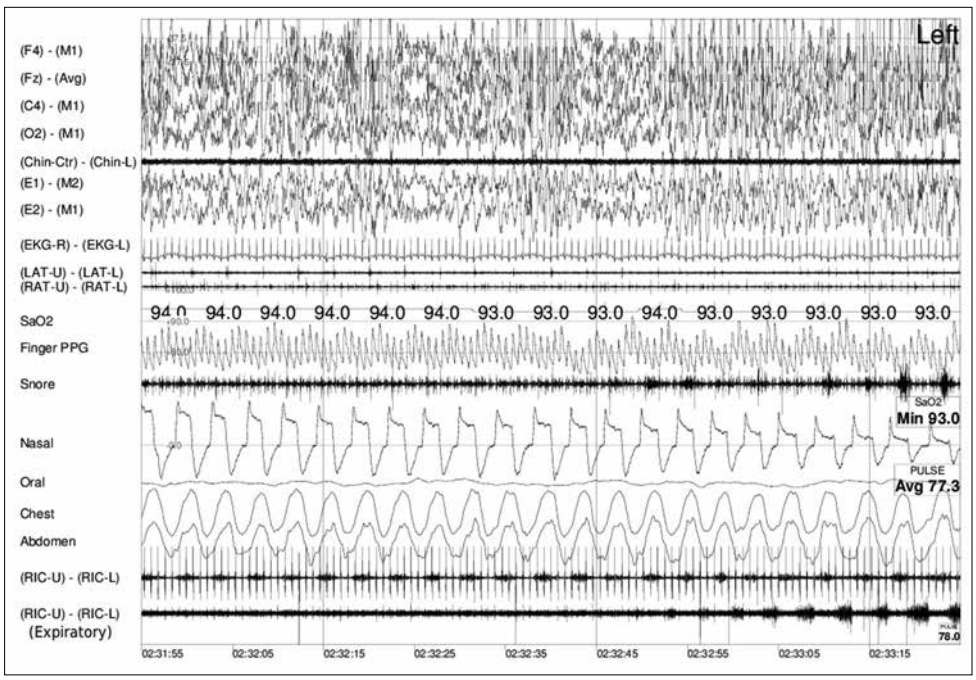

Figure 1: Inspiratory flow limitation. Example of a recording of "inspiratory flow limitation" as indicated by the monitoring of nasal airflow through the "nasal cannula-pressure transducer." No apnea or hypopnea is present in the segment, but the sleep EEGs (4 channels-1-4 from top) indicate the presence of cyclic alternating pattern phase A2, indicative of NREM sleep disturbances. The recording of the nasal cannula measuring airflow exchange is presented on channel 14 from top The figure shows the presence of flow limitation with the presence of an abnormal wave contour: instead of a smooth round wave contour, there is a truncation of the wave contour during inspiration (per convention; up part of the wave), there is no mouth breathing (oral thermistor - channel 15 from top), and chest and abdomen inductive plethysmography bands are indicating breathing efforts. The figure shows a worsening of the flow limitation from left to right with decrease in amplitude of the wave. This worsening is associated with the occurrence of snoring (channel 13 from top). However, with onset of snoring, there is another event occurring: nasal cannula-pressure transducer is an unreliable way to measure expiratory flow, and if an expiratory flow limitation occurs a different variable must be monitored. Normally expiration is mostly "passive" with the absence of involvement of expiratory muscles (monitored on channel 19 from top-bottom channel) as can be seen there is the appearance of "active" contraction of expiratory muscles as seen on the right of the figure. There are simultaneous changes in the inspiratory wave contour with reduction of its amplitude and appearance of expiratory efforts. The oxygen saturation (channel 11 from top) changes somewhat with SaO_2 going from 94% to 93%, but this 1% change is not a change monitored in any international atlas. Channel 12 monitors the finger photoplethysmography, i.e., the finger vaso-constriction, per convention the curve is presented such as an increase in vasoconstriction indicative of sympathetic activation is associated with a downward displacement of the curve. As can be seen in association with occurrence of snoring and other flow changes, there is a change of the photoplethysmography curve indicative of repetitive stimulation of the sympathetic nerve with snoring, and with swings of the photoplethysmography more pronounced at the right of the figure indicative of a larger stimulation of the sympathetic tone associated with worsening of inspiratory and expiratory flow limitation. None of these changes are taken into consideration in the international scoring manuals looking at abnormal breathing during sleep, despite the fact that many disruptions occur and worsen with snoring.

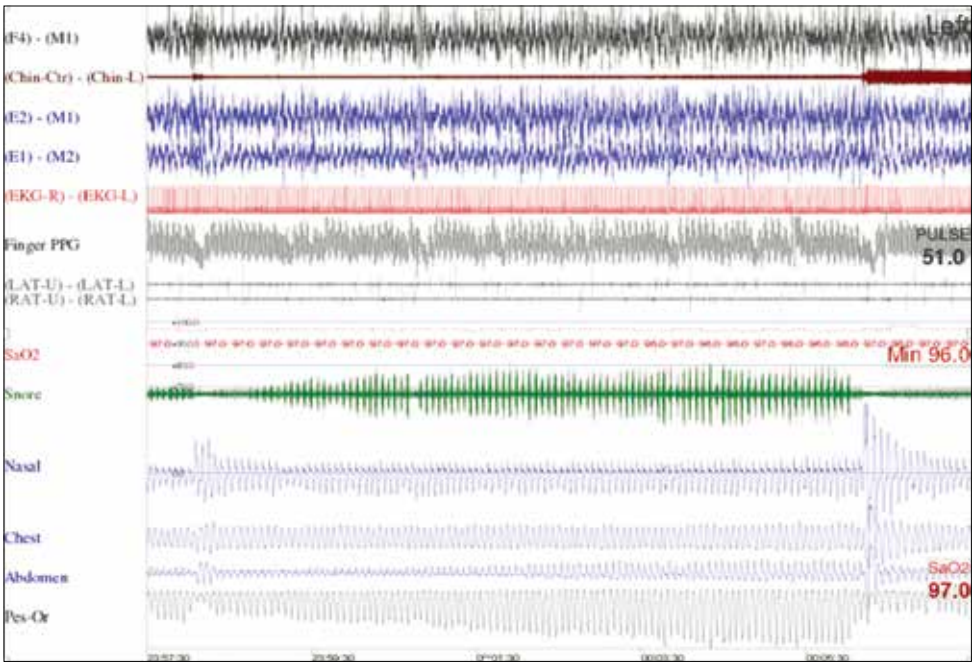

Figure 2: Example of abnormal increased inspiratory effort measured with esophageal manometry [Pes = esophageal pressure].This recording present 15 min of continuous recording. Fourteen channels of the recording have been selected for presentation of the figure from top to bottom. Electroencephalography, Chin electromyography, 2 eye movements, finger photoplethysmography (with sympathetic activation toward the bottom of figure), 2 leg electromyography, pulse oximetry with saturation reading, snore indicated by neck microphone measuring power, nasal cannula-pressure transducer wave contour, chest and abdomen plethysmographic bands, and esophageal manometry recording (bottom). Esophageal pressure has been calibrated before the beginning of recording. The negative peak is per convention placed toward the bottom of the recording. The end of the recording probe is placed in the lower esophagus. This segments of recording show a progressive increase in inspiratory efforts with peak esophageal pressure becoming more and more negative during the following 10 min. There is the presence of inspiratory flow limitation when looking at the nasal cannula wave contour, but no change indicating increase in effort. The electroencephalography analysis indicates the presence of cyclic alternating pattern phase A2, but a clear electroencephalography arousal is only noted at the end of the recording in association with return to normal breathing and important chin electromyography discharge. The investigation of the photoplethysmography indicates that during the entire segment, there are clear indications of several episodes of sympathetic activation that correlate with the cyclic alternating pattern phase A2 bursts, but these short arousals are not sufficient to lead to reopen the airway. A respiratory event- related arousal will be scored at the end of the event in association with the more than 3 s electroencephalography arousal, but the scoring will ignore the long abnormal breathing segment, the calculation of the "flow limitation" gives a better view of the duration and amount of disturbance than calculation of the respiratory -related arousal, moreover "respiratory event related arousals" are not taken into consideration when the apnea-hypopnea index is calculated, the figure indicates the limitations of many scoring systems.

Tachypnea

Definition

An increase in RR above that seen during quiet unobstructed breathing: by a minimum of 3 breaths/min in NREM sleep or 4 breaths/min in REM sleep for ≥30 s. After 24 months of age, normal RR is 16–18 breaths/min in NREM sleep and 17–19 breaths/min in REM sleep. No associated changes in oxygen saturation, Pes, or EEG are required. It is based on the definition: Tv × RR = minute ventilation. If the RR increase and oxygen saturation stay stable, this indicates a compensation for decrease in tidal volume and indication of abnormal breathing during sleep.

Mouth breathing

Studies on mouth breathing have shown that normal controls usually spend 4% of total sleep time with mouth breathing, and studies in children showed a maximum amount of mouth breathing of 10% of total sleep time.[29-31] Mouth opening is associated with a backward and downward displacement of the mandible and the tongue and has been shown to increase the propensity to UA collapse.[32] posterior and inferior movement of the mandible may shorten the UA dilator muscles located between the mandible and hyoid and compromise their contractile force by producing unfavorable length/tension relationships in these muscles. One explanation for this phenomenon is that jaw opening is associated with a posterior movement of the angle of the jaw, which compromises the oropharyngeal airway diameter. Open mouth breathing is associated with an increase in pharyngeal length. The faster airflow generated by the longer and narrower UA may increase the negative intraluminal pressure during inspiration and facilitate collapse of the UA.

Conclusion

We have learned a large amount about SDB over time. We know that certain groups of children are at greater risk of abnormal breathing during sleep; including obese children,

when an increase of BMI by 1 kg/m^2 above the upper limit of normal is associated with a 12% increase in risk for OSA, and children born prematurely,[33] and as mentioned above change in oral-facial growth that will begin with birth. this growth change may be related not only to genetic factors (such as those involved in teeth development or oral development) but also to environmental factors, particularly involving functions such as sucking, swallowing, speech development, and nasal breathing.[34,35] UA allergies with impact on normal breathing and leading to increase in local inflammatory factors have also been considered risk factors. The frequency of SDB related to UA collapse during sleep has oscillated; initially, it was considered as low as 2%–4% of the general population, but with better recognition of the abnormal breathing during sleep, frequency increased; currently, a conservative estimate would be 7%, but some studies go to a frequency as high as 11% of the general children population. Moreover, there is an agreement that certain ethnic groups are at greater risks. more particularly, African-American and their tendency to increase BMI more frequently than Caucasians (and the role of socioeconomic factors have not been well identified) and Far East Asian with the very different orientation of the maxilla at birth compared to Caucasians. However, the main issue is to recognize children with abnormal breathing as early as possible and to know how to give value to indicators seen in testing.

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Conflicts of interest

There are no conflicts of interest.

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Viruses and Hospitalization for Childhood Lower Respiratory Tract Infection in Malaysia: A Prospective Study

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Abstract

Context: Viruses are the main causes of acute lower respiratory tract infections (ALRIs) in childhood and its impact on hospital admission is largely unknown. **Aims:** The aim of this study is to determine (a) virus detection, (b) risk factors for admission, particularly virus detection, and (c) differential clinical responses to viral infections, in children attending pediatric emergency department (PED) with an ALRI in Malaysia. **Subjects and Methods:** This prospective study included children ≤2 years who presented to PED between September 1, 2010, and March 6, 2012, with features of lower respiratory tract infection. Nasopharyngeal aspirates (NPAs) were tested using a multiplex polymerase chain reaction (PCR) for 11 respiratory viruses. **Results:** Two hundred children were recruited in the study. Two-thirds (65.5%) of them were admitted. NPA-PCR was positive in 54% of all patients: 50.4% of those admitted and 60.9% of those discharged. The most common viruses detected were respiratory syncytial virus (RSV) (49.1%), rhinovirus (30.6%), and parainfluenza viruses (12.0%). Five patients had mixed infections. RSV detection was associated with previous history of wheeze (odds ratio, 2.05 [95% confidence interval 1.06, 4.00]). Viruses were detected in all severely ill patients and patients with apnea. Multivariate analysis showed that virus detection was not associated with the need for admission, but female sex, lack of breastfeeding and, attending nursery were associated with hospitalization. **Conclusions:** Half of the children who presented to the emergency room with ALRI had viruses detected in their NPA. There was no association between virus detection and hospitalization. RSV was associated with history of wheeze. Female gender, lack of breastfeeding, and nursery attendance were associated with hospitalization.

Keywords: Acute respiratory infections, etiology, bronchiolitis, children, emergency department, Malaysia, pneumonia, viruses

Introduction

Viruses are the main cause for acute lower respiratory tract infection (ALRI), whether in the developing or developed countries. Factors determining hospitalization are important for health and economic reasons. Many studies focus on etiology of ALRI in admitted patients,[1-3] but few studies focus on children attending the pediatric emergency department (PED) alone[4,5] to determine the factors associated with admission, especially positive virus detection and coinfections.

The aim of this study was to determine the risk factors for admission in children attending the PED with an ALRI.

Subjects and Methods

Ethics

Ethical approval was obtained from the hospital's Medical Ethics Committee (No. 996.3) and informed parental consent was obtained. However, no assent was obtained from patients aged above 7 years. Patients' information was anonymized and de-identified before analysis.

Study site

This study was conducted in a 1068-bedded tertiary general hospital in Kuala Lumpur, Malaysia, which serves an urban population of 1.7 million. In our center, we have 100 pediatric beds, including a 10-bed Pediatric Intensive Care Unit.

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Study type and patient selection

This is a prospective study of children, 2 years old and younger, who presented to the PED, between September 1, 2010, and March 6, 2012, with ALRIs. ALRI was defined as symptoms (either cough or shortness of breath) and signs (wheeze and/or crepitation and/or recession and/or respiratory distress) of a lower respiratory tract infection. Children with a diagnosis of asthma and those attending the PED during the weekends were excluded from the study.

Data collection

Basic demographic data including comorbidities, birth history, concurrent medications, family history of asthma and atopy, antenatal and postnatal exposure of cigarette smoke, breastfeeding (total duration and exclusive), history of wheezing, current weight, presenting symptoms and signs, and outcome were collected prospectively, using a preprepared data collection sheet.

Specimen processing

All children had nasopharyngeal aspirates (NPAs) collected by trained nurses after nebulization of either 3% NaCl or salbutamol to enhance the chance of virus detection. The exact choice was at the discretion of the attending doctor samples being kept at −20°C before testing. RNA was extracted from 140 µl of each sample using QIAmp Viral RNA Mini Kit (QIAGEN, Germany) following the manufacturer's protocol and eluted in 50 µL of sterile water. Complementary DNA was synthesized using Superscript III RT (Invitrogen, USA). Each reaction was carried out with 0.25 µL of 20X reverse transcriptase-primer mix (500 µg/ml), 1 µl of dNTPs (10 mM each), and 3 µL of RNA template (1 µg/µL) and heated at 65°C for 5 min. The solution was equilibrated at 4°C and mixed with 1 µL of 5X first-strand buffer and 0.25 µL of 0.1 M DTT and incubated at 25°C for another 5 min. Finally, 0.25 µL (50 units) of Superscript II Reverse transcriptase was added to the solution with a final volume of 5 µL, which was then incubated at 50°C for 1 h, before inactivation at 70°C for 15 min. The final products were stored at −20°C until testing using a multiplex polymerase chain reaction (PCR) assay, RespiDetect (Tropical Infectious Diseases Research and Education Centre, Malaysia), following the manufacturers' protocol. This assay is based on dual-priming oligonucleotide technology and detects 11 respiratory viruses: respiratory syncytial virus (RSV), influenza A and B, parainfluenza virus 1–3, adenovirus, human metapneumovirus, human rhinovirus (HRV), coronavirus, and bocavirus. PCR products of the expected size were identified by gel electrophoresis.

Definitions of variables and outcomes

The main outcome measured was admission versus discharge as decided by the PED physician. Oxygen is usually supplied if the saturation is <95% in room air or if there are signs of respiratory distress. Each patient's weight was measured and computed into *Z* score using gender- and age-specific cutoff points proposed by the World Health Organization guidelines.[4]

Life-threatening pneumonia was defined as children who require intensive care treatment and/or noninvasive ventilatory support, for example, bilevel continuous positive airway pressure or high-flow nasal cannula oxygen. Low birth weight was defined as birth weight <2.5 kg. Prematurity was defined as gestation <37 weeks. Environmental tobacco smoke (ETS) exposure was defined as presence of any smoker in the family or caregiver's household.

Statistics

The data were analyzed using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Data were described using percentage, median, and interquartile range (IQR). The Chi-squared test or Fisher's exact test (where appropriate) was used to perform univariate analysis between the clinical factors and the outcome, i.e. hospitalization or not. Factors included in univariate analysis were as follows: age, gender, presence of any comorbidity (such as chronic lung disease, heart disease, and chronic liver and gut disease), family history of atopy, prematurity, birth weight, current weight percentile <−2 standard deviations, any breastfeeding, attending nursery or daycare, exposure to ETS (antenatal and postnatal), positive respiratory virus PCR result, and PCR positive for more than one virus. Binary logistic regression was performed with factors identified in univariate analysis with $P < 0.10$. In the final analysis of results, $P < 0.05$ was considered statistically significant. Association was presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

Altogether, 255 children were recruited in the study. Thirty-two NPAs were misplaced and 23 were excluded due to a possible asthma. Finally, 200 episodes of infection were analyzed [Figure 1].

Demographic data

Characteristics of the patients are shown in Table 1. The median age was 8 months with a male predilection. The ethnic distribution is representative of Malaysia. The main comorbid diseases in these children were previous pneumonia ($n = 21$, 58.3%) and cardiovascular disease ($n = 4$, 11.1%). The median (IQR) gestational age of the children who were premature was 34 weeks (33–35 weeks). There was a significant exposure to both antenatal and postnatal ETS exposure. More

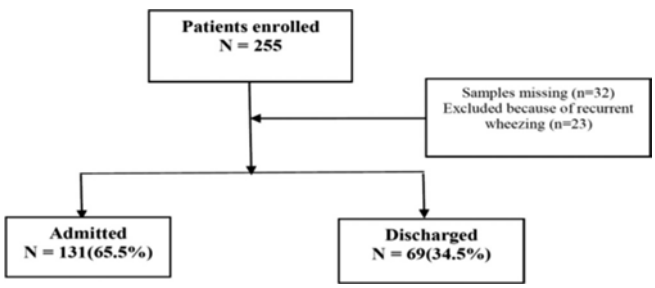

Figure 1: Study flow.

Table 1: Demographic characteristics between those admitted versus discharged

Demographic characteristics	All children, *n* (%)	Admitted (*n*=131), *n* (%)	Discharged (*n*=69), *n* (%)	*P*	OR/Z score	95% CI
Age*						
Median (range), years	0.7 (0-2.3)	0.7 (0-2.3)	0.6 (0.1-1.7)	0.08	Z=−1.75	NA
Sex*						
Male	132 (66.0)	80 (6.01)	52 (75.4)	0.04	0.81	0.67-0.99
Female	68 (34.0)	51 (38.9)	17 (24.6)			
Ethnicity*						
Malay	170 (85.0)	117 (89.3)	53 (76.8)	0.04	-	-
Chinese	6 (3.0)	4 (3.1)	2 (2.9)			
Indians	22 (11.0)	10 (7.6)	12 (17.4)			
Others	2 (1.0)	0	2 (2.9)			
Comorbidities						
Yes	36 (17.5)	26 (19.8)	10 (14.5)	0.35	1.13	0.89-1.42
No		105 (80.2)	59 (85.5)			
Premature						
Yes	19 (9.5)	10 (76.9)	9 (13.0)	0.22	0.79	0.51-1.22
No		120 (23.1)	60 (76.0)			
Nursery*						
Yes	105 (52.5)	77 (59.2)	28 (41.2)	0.016	1.29	1.04-1.59
No		53 (40.8)	40 (58.8)			
Birth weight						
Median (IQR)	3.0 (2.8,3.3)	3.0 (2.8,3.3)	3.0 (2.7,3.3)	0.46	Z=-0.69	NA
Weight ≤−2SD						
Yes	37 (18.5)	27 (21.8)	10 (14.9)	0.23	1.16	0.92-1.46
No		97 (78.2)	57 (85.1)			
Family history of atopy						
Yes	59 (29.5)	37 (29.1)	22 (33.3)	0.55	0.83	0.43-1.58
No		90 (70.9)	44 (66.7)			
Environmental tobacco smoke						
Antenatal						
Yes	85 (43)	54 (41.5)	31 (46.3)	0.53	0.94	0.76-1.15
No		76 (58.5)	36 (53.7)			
Postnatal						
Yes	111 (55.5)	56 (43.1)	30 (43.5)	0.82	0.98	0.80-1.20
No		74 (56.9)	39 (56.5)			
Breastfeeding (any)*						
Yes	152 (76.9)	93 (72.7)	59 (88.1)	0.01	0.75	0.62-0.91
No		35 (27.3)	8 (11.9)			
Diagnoses*						
Bronchiolitis/others	138 (69)	81 (61.8)	57 (82.6)	0.002	0.34	0.16-0.69
Pneumonia	62 (31)	50 (38.2)	12 (17.4)			
PCR for viruses						
Positive	108 (54)	66 (50.4)	42 (60.9)	0.16	0.87	0.71-1.06
Negative	92 (46)	65 (49.6)	27 (39.1)			
PCR positive for >1 virus						
Yes	5 (2.5)	3 (2.3)	2 (2.9)	0.79	0.79	0.11-6.75
No	195 (87.5)	128 (87.7)	67 (87.1)			

*Significant at $P<0.01$ and included into the logistic regression analysis. OR: Odds ratio, PCR: Polymerase chain reaction, SD: Standard deviation, IQR: Interquartile range, CI: Confidence interval, NA: Not available

than two-thirds of the children (77%) were breastfed. The most common diagnosis was bronchiolitis (69%) and two-thirds of patients (65.5%) were admitted.

Pathogen detection

NPA-PCR was positive in 54% of children: 50.4% of those admitted (*n*=66/131) and 60.9% of those discharged (*n*=42/69). The NPA was positive in 52% (*n* = 72/138) of children with bronchiolitis and 58% (*n*=36/72) of children with pneumonia. Common viruses detected were RSV (*n* = 53, 49.1%), rhinovirus (*n* = 33, 30.6%), and parainfluenza virus (*n* = 13,

12.0%) and altogether these represented 91.7% of all the viruses detected. Five patients (2.5%) had two viruses detected in NPA: RSV + bocavirus (1), RSV + influenza A (1), RSV + HRV (1), HRV + bocavirus (1), and HRV + influenza B (1). Of those admitted patients, 119 NPA samples were sent for bacterial culture and 44 patients had a positive culture (37%).

Risk factors for admission

Virus detection was not associated with hospitalization [Table 2]. In Univariate analysis, factors possibly associated with the need for admission were young age, female gender, Malay ethnicity, attending nursery, diagnosis of pneumonia and not being breastfed [Table 1]. Binary logistic regression identified that female gender, attending nursery, and not being breastfed were independent risk factors for hospitalization [Table 3].

Clinical responses to viral infections

The following symptoms were not associated with virus infection: fever (P = 0.45, OR 0.79 [95% CI 0.44, 3.42]), rhinitis (P = 0.08, OR 1.87 [95% CI 0.93, 3.75]), shortness of breath (0.65, OR 0.84 [95% CI 0.46, 1.52]), presence of wheezing (P = 0.82, OR 1.06 [95% CI 0.59, 1.91]), and diarrhea (P = 0.35, OR 2.06 [95% CI 0.52, 8.19]).

Only 2 cases of apnea were admitted during this study and RSV and rhinovirus accounted for these two cases. There was a significant association between the symptom of vomiting and virus detection (P < 0.001, OR 4.67 [95% CI 1.94, 11.24]). All the six children who had life-threatening pneumonia had viruses detected in their NPA (influenza [n = 1], RSV [n = 1], rhinovirus [n = 2], rhinovirus + RSV [n = 1], and bocavirus [n = 1]), P = 0.05 (OR 8.37 [95% CI 0.96, 255.2]). None of the children were intubated for their infection and there were no deaths.

Table 2: Odds ratio of admission for nasopharyngeal aspirates positive viral cases

Virus	Positive and admitted/total positive (%)	*P*	OR	95% CI
Any positive	108/181	0.157	0.865	0.708-1.056
RSV	30/53 (56.6)	0.112	0.824	0.635-1.068
Rhinovirus	23/33 (70.0)	0.579	1.078	0.838-1.386
Parainfluenza	7/13 (53.8)	0.377§	0.812	0.486-1.357
Influenza	5/7 (71.4)	1.000§	1.094	0.677-1.768
Bocavirus	3/5 (60.0)	1.000§	0.914	0.914-1.883
hMPV	1/2 (50.0)	1.00§	0.762	0.190-3.056
Adenovirus	0/1 (0.0)	0.330§	-	-

§Fisher's exact test. RSV: Respiratory syncytial virus, hMPV: Human metapneumovirus, OR: Odds ratio, CI: Confidence interval

Table 3: Binary logistic regression analysis of factors that were significantly associated with admission to hospital

	OR	95% CI	*P*
Female	2.10	1.047-4.202	0.037
Breastfeeding	0.397	0.169-0.933	0.034
Attending nursery	2.087	1.119-3.891	0.021

OR: Odds ratio, CI: Confidence interval

Clinical responses to specific viruses

Children ≤6 months were not more likely to be infected with RSV (P = 0.25, OR 1.49 [95% CI 0.79, 2.82]). Both HRV detection (P = 0.16, OR = 2.03 [95% CI 0.83, 4.96]) and RSV detection (P = 0.40, OR = 0.75 [95% CI 0.39, 1.45]) were not associated with current wheezing. However, RSV detection was significantly associated with a previous history of wheeze (P = 0.03, OR 2.05 [95% CI 1.06, 4.00]). This association was not seen with HRV (P = 0.85, OR 1.17 [95% CI 0.54, 2.0].

Discussion

In this prospective study, half of the young children presenting to the PED with ALRI were positive for a respiratory virus, but there was no significant association between virus detection and hospitalization. However, all six severely ill children had viruses detected in their NPA. We found three significant clinical factors associated with admission: female sex, nursery attendance, and lack of breastfeeding. RSV, and not HRV, was detected more frequently in children with a previous history of wheezing. Symptom of vomiting was significantly associated with viral detection.

This study was conducted in a tertiary hospital, located in an urban city, with a high attendance of children presenting with respiratory infections, and only young children with ALRI were included. All samples were NPAs, the optimal specimen for viral detection.[6,7] Half of the samples (50.7%) were positive for a virus and 2.5% had mixed viral infections. A retrospective study from the Netherlands, done in the accident and emergency department during two winter seasons, showed that 82% of 274 samples were positive for a single virus and 23% had mixed viral infections.[5] In another study from France about childhood upper and lower respiratory tract infections, 89% of samples were positive.[4] A possible reason for the extremely high positivity rate in the study from the Netherlands was the sampling period, when viral infections would be at its peak. In a tropical climate like Malaysia, it was shown that RSV had its peak season from September to December but generally viruses are prevalent throughout the year.[8,9] In a study in Beijing, China, which included both inpatients and outpatients, using reverse transcriptase PCR to detect viruses, 61.7% of patients were positive for a virus, a rate similar to ours.[10] RSV was the most common virus detected in those who were admitted while influenza was most common in those who were discharged, and being positive for any virus was not associated with admission (69% in those admitted versus 54% in those discharged).[10] In another inpatient-based study, conducted in the Philippines, involving 819 children admitted with severe pneumonia and using PCR to detect viruses, the positivity rate was also 61% with HRV and RSV being the most common viruses detected.[11] This study had a low mixed infection rate of 8%,[11] compared to other studies which found mixed viral infection rates of 14%–40%.[3,12,13] In

a review of published studies, viruses were found in 43%–67% of children with community-acquired pneumonia in children, although the detection rate will be affected by many factors including type and extent of molecular assay used, season, sample population, indications for testing, and methods of sample collection and processing.[14,15]

The most common viruses detected in our study were RSV, HRV, and parainfluenza virus, similar to the other studies, both in Asia and Europe.[5,10,11] RSV but not rhinovirus was associated with previous history of wheezing, but neither HRV nor RSV was significantly associated with current wheezing. This finding differed from that in the Netherlands, where prior treatment with steroids and salbutamol was associated with HRV.[5] Both HRV and RSV were reported to be associated with increased risk for future wheezing. RSV is more likely an "inducer" by its neuroimmune effect on the airways and not via allergic sensitization whereas HRV is a "trigger" inducing release of chemokines and cytokines that triggers the allergic pathway in a child with a predisposition to asthma.[16] As for severity of disease, while in this study neither RSV nor any other virus was associated with severity of illness, all children who had severe respiratory compromise were virus positive. In the Netherlands, HRV was associated with severe disease while RSV was inversely associated with severity of disease.[5] HRV-C is known to be associated with lower respiratory tract infections while HRV-A and B is associated with upper respiratory tract infections.[17] We did not include the HRV in this study. However, one patient who was HRV positive had a severe ALRI requiring noninvasive ventilation support. There was evidence that HRV might not be all benign.[5]

The role of mixed viral infections could not be evaluated in this study due to the small number of positive samples. Nonetheless, globally, its impact on ALRIs was also not clear.[18] This is due to the high sensitivity of PCR, which may detect asymptomatic infections or low levels of virus from recent, resolved infections, hence resulting in over detection of "innocent" pathogens, especially rhinovirus.[19] Nevertheless, some studies showed an association between mixed viral infections with increased severity of illness.[10,12]

The other important finding of our study was the three clinical factors significantly associated with the need for admission: female gender, nursery care, and lack of breastfeeding. Other factors such as age and exposure to ETS were not significant. The protective effect of breastfeeding against ALRI confirmed findings in other studies.[2,20] Care outside the home, if more than 6 children are in attendance, was shown to be associated with hospitalization for an ALRI.[21]

Finally, in this study, children with a clinical presentation of vomiting were more likely to have viruses detected in their NPA. Vomiting is a known sign of an infection in a child and is not specific to the gastrointestinal system.[22]

The main strength of this study is that it is a prospective study and looks at the impact of viruses in the Emergency Department of a developing country.

Limitations to this study included the small sample size with only 200 patients recruited as patients who attended during the weekends were excluded from the study. We recognize the possible impact of bacterial–viral infections on increasing severity of illness; however, we cannot report on this as only children who were admitted had bacterial cultures done. This study was also done in a tertiary hospital, and hence, the results may not be extrapolated to the rest of Malaysia.

Conclusions

Detection of viruses in children presenting to the PED was not associated with hospitalization for an ALRI. About half of the children presenting to PED were positive for a respiratory virus. All children who were severely ill, requiring noninvasive ventilation, had viruses detected in their NPA. Three clinical factors significantly associated with the need for admission were being female, attending nursery, and lack of breastfeeding. RSV but not HRV was detected more frequently in children with a previous history of wheeze.

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Conflicts of interest

There are no conflicts of interest.

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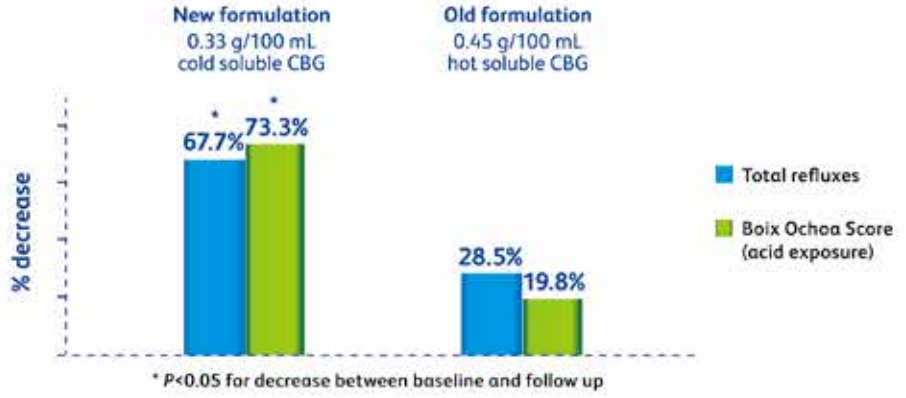

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Reference: Georgieva M, Manios Y, Rasheva N, Pancheva R, Dimitrova E, Schaafsma A. Effects of carob-bean gum thickened formulas on infants' reflux and tolerance indices, *World J Clin Pediatr*, 2016 February 8; 5(1): 118-127.

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Balanced nutrition†

- Provide important nutrients that support healthy growth and development, including DHA, AA, nucleotides, selenium, taurine, choline and more

† Balanced nutrition for infants from 0-6 months. From 6 months onwards, infants need complementary foods to achieve balanced diet.

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Breastfeeding is the best nutrition for healthy growth and development of babies. Mothers should receive guidance on proper maternal nutrition in order to help sustain an adequate supply and quality of breast milk. Unnecessary introduction of bottle-feeding, partially or fully, or of other complementary foods and drinks may have a negative impact on breastfeeding, which may be irreversible. Mothers should consult their doctor and consider the social and financial implications before deciding to use breast milk substitutes or if they have difficulty breastfeeding. Usage, preparation and storage instructions of breast milk substitutes or of other complementary foods and drinks should be followed carefully as improper or unnecessary use may pose a health hazard.

For medical professionals' reference only.

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HERMES
Harmonised Education in Respiratory Medicine for European Specialists

A chance to obtain an international qualification in paediatric respiratory medicine

The second joint ERS/APPS examination will be held on 27 October 2017 in Bengaluru, India. There will be two parts:

- Part I: ERS HERMES^ Examination in Paediatric Respiratory Medicine – 3 hours
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Candidates who pass part I will be awarded the European Diploma in Paediatric Respiratory Medicine by ERS.
Candidates who also pass part II will be awarded Diplomate of APPS.

There will be one day pre-exam crash course to be held on 26 October 2017 in Bengaluru, India.

Fees:

- Pre-exam crash course: USD 100
- Examination: USD 600

Application:

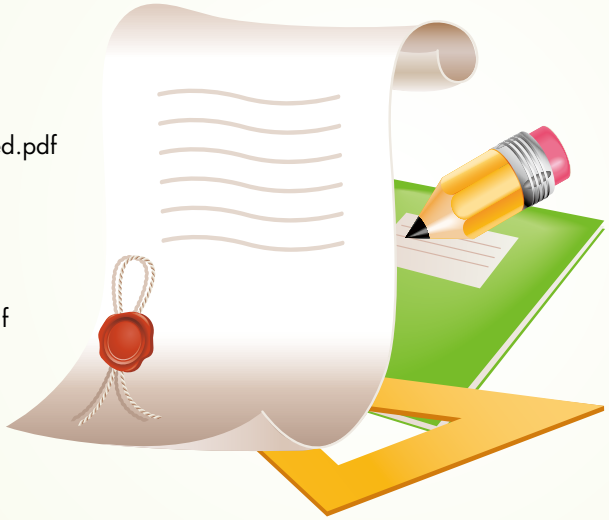
- Candidate must send in (i) application form; (ii) support letter from council members or office bearers of APPS; (iii) payment receipt to apps.medisociety@gmail.com
- Deadline of Application: 15 August 2017

Eligibility Criteria:

- Specialists in paediatric respiratory medicine recognised in their respective home countries and endorsed by council members or office bearers of APPS.

Useful Links:

- Syllabus – http://hermes.ersnet.org/images/paediasyllabus_HERMES_Breathe_Paediatric_Syllabus.pdf
- Blueprint – http://hermes.ersnet.org/images/PRM%20Blueprint_revised.pdf
- Handbook – http://www.ersbookshop.com/ers-handbook-of-paediatric-respiratory-medicine-119-p.asp
- Sample Test – http://www.ers-education.org/MOS_R1/MosPub/HERMES_Test/index.html
- Practical Tips – http://hermes.ersnet.org/images/getting%20ready.pdf



Enquiry:

Please contact Ms. Melissa Leung by email:
apps.medisociety@gmail.com

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- Skin and Allergy

Plenary Lectures and Symposia

- Allergy
- Critical Care
- Infection
- Interventional Pulmonology
- Lung Function
- Respirology
- Skin
- Sleep

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Ms. Katherine Cheung, *Kwong Wah Hospital*
Professor Zen-kong Dai, *Kaohsiung*
Ms. Robin Glass, *Washington*
Dr. Mark Goh, *Singapore*
Professor Christian Guilleminault, *California*
Professor Ellis Hon, *The Chinese University of Hong Kong*
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CME, CNE and CPD points will be applied for the meeting.

Offsite Courses Co-organizers

- Academy of Orofacial Myofunctional Therapy
- Asian Paediatric Pulmonology Society
- Department of Paediatrics, Kwong Wah Hospital
- Department of Physiotherapy, Kwong Wah Hospital

Supporting Organizations

- Asian Paediatric Pulmonology Society
- Chinese Paediatric Interventional Pulmonology Society
- Hong Kong College of Paediatricians
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Important Notice:

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Programs / schedules may be subject to change