Obstructive sleep apnea
Is it time for personalized medicine?

Catherine Kier, MD
Professor of Clinical Pediatrics
Division Chief, Pediatric Pulmonary, and Cystic Fibrosis Center
Director, Pediatric Sleep Disorders Center
SUNY Stony Brook
No disclosures
Objectives

• At the end of this session, the participant would be able to

• Discuss tools and ways to assess the different traits contributing to OSA in a given individual

• Discuss and provide options for diagnosis and treatment best suited for individual patients, toward personalizing the treatment of OSA
Pathophysiology of OSA

Structural factors
- Adenotonsillar hypertrophy
- Craniofacial abnormality
- Obesity

Neuromotor tone
- Cerebral palsy
- Genetic diseases

Other factors
- Genetic
- Hormonal
- ?

OSA
OSA is a multifactorial disorder

Environment:
- Nutrition
- Passive smoking
- Physical activity
- Intellectual activity
- Respiratory infections

OSA Severity:
- OAHI
- Nadir SpO2
- Cumulative desaturation index
- Respiratory arousal index
- Alveolar hypoventilation
- Intra-thoracic pressure swings

Individual Susceptibility:
- Apolipoprotein E
- Single nucleotide polymorphisms for genes regulating inflammation and oxidative stress

Spectrum of OSA is complex

Sleep-related breathing disorder continuum

Snoring → UARS → Hypopneas → Apneas → Obesity-Hypoventilation Syndrome → Apneas

Obstructive sleep apnea should be considered as a continuum of disease, i.e., a spectrum of abnormalities from snoring to obesity-hypoventilation syndrome.
Wish we all could have a good night sleep!

• Rechtschaffen (1971) “if sleep does not serve an absolute vital function, then it is the biggest mistake the evolutionary process ever made...”

• Neuroplasticity
  - sleep linked to memory and learning
  - pediatric sleep disorders in the first 5 years of life associated with special educational need at 8 years of age

*Pediatrics* 2012;130:634–642
Recommended hours of sleep in children

• Ages 4-12 months: 12-16 hours (including naps)
• Ages 1-2 years: 11-14 hours (including naps)
• Ages 3-5 years: 10-13 hours (including naps)
• Age 6-12 years: 9-12 hours
• Age 13-18 years: 8-10 hours

• a consensus statement of the American Academy of Sleep Medicine
• endorsed by the American Academy of Pediatrics
• Sleep is essential for optimal health

Adverse consequences not just to immediate but to long-term health (adulthood)

- Pulmonary hypertension
- Cor pulmonale
- Endothelial dysfunction
- Insulin resistance
- Dyspilidemia
- Nocturnal enuresis
- Increased healthcare utilization
- Neurocognitive impairment
- Hyperactivity
- Attention deficits
- Concentration difficulties
- Impulsivity
- Excessive daytime sleepiness
Mechanisms of OSA

upper airway narrowing
- adenotonsillar hypertrophy
- obesity

upper airway collapsibility
- decrease in muscle tone: neuromuscular diseases/cerebral palsy
- airway inflammation: rhinitis
- obesity

Airway patency
Starling resistor model

• when pressure outside the collapsible segment is greater than within the segment

• Children with OSA have significantly more collapsible UA with elevated $P_{crit}$ (less negative) during sleep
Assessment of airway collapsibility

• Complicated to perform – application of negative nasal pressure to sleeping patient
• Or needs equipment: acoustic pharyngometry
Surrogate markers for airway collapsibility

- inspiratory airflow limitation (pressure transducer)
- No difference in non-REM
- but in REM, OSA children with higher % inspiratory flow limitation (decreased compensatory neuromuscular response to upper airway obstruction)
- improved after adenotonsillectomy

Sleep endoscopy

• Should it be routinely performed prior to adenotonsillectomy? (so multilevel obstruction be identified)
  • N=37
  - 33 with upper airway obstruction
  - 28 adenotonsillectomy,
  - 3 adenoidectomy, 2 tonsillectomy (91% success rate)
  - 4 non-surgical (CPAP/orthodontics)
• Controversial – routine (implications on resources and workloads)
• Mainly used for assessment of:
  • Residual OSA, post-AT, complicated OSA (e.g. craniofacial abnormalities, cerebral palsy, Down’s)


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5743164/
Brodsky tonsillar grading scale

Grade 1: tonsil occupies ≤25% of the oropharyngeal width to midline

Grade 2: Tonsil occupies 26%–50%

Grade 3: Tonsil occupies 51%–75%

Grade 4: Tonsil occupies >75%
Spectrum of pediatric obstructive sleep disordered breathing

• Primary snoring
  • habitual snoring for more than 3 nights per week without apneas, hypopneas, frequent arousals or gas exchange abnormalities (prevalence 7.45%)

• Upper airway resistance syndrome (UARS)
  • snoring, increased work of breathing and frequent arousals, without recognizable obstructive events or gas exchange abnormalities

• Obstructive hypoventilation
  • snoring plus elevated end-expiratory carbon dioxide partial pressure in the absence of recognizable obstructive events

• OSA syndrome
  • recurrent events of partial or complete upper airway obstruction (hypopneas, obstructive or mixed apneas) with disruption of normal oxygenation, ventilation and sleep pattern (prevalence 1% to 5%)
snoring with flow limitation on the nasal pressure airflow transducer – consistent with upper airway resistance
Obstructive hypopneas – snoring followed by reduced flow; presence of breathing Effort but paradoxical; desaturations with recovery at the end of hypopnea
Obstructive apneas - snoring and increase work of breathing followed by cessation of airflow; paradoxical breathing respiratory effort; desaturations and recovery at the end of each apnea.
Anatomical features → upper airway narrowing

- Micrognathia
- Macroglossia
- Midface hypoplasia

Treacher Collins syndrome, Crouzon syndrome, Apert syndrome, Pierre Robin sequence, achondroplasia, trisomy 21, Beckwith Wiedemann syndrome, mucopolysaccharidoses
Epidemic of obesity

- About 50% of overweight/obese children have obstructive sleep apnea (OSA) compared to up to 6% of normal weight children
  - Sleep 2014; 37:943-9

- every 1 kg/m2 increase in body mass index (BMI) above the mean for age and sex increases the risk of developing OSA by 12%
Obesity contributing to OSA in mechanical ways

- Fatty infiltrates within the upper airway (UA) structure and neck $\rightarrow$ UA narrowing $\rightarrow$ pharyngeal collapsibility
- Abdominal visceral fat limits diaphragmatic descent (especially when supine)
- Adipose tissue in chest wall - impair lung compliance $\rightarrow$ hypoventilation, atelectasis and VQ mismatch
OSA and inflammation evidences

• Nasal nitric oxide elevated in OSA and primary snoring (marker of airway inflammation)

• H2O2 in morning exhaled breath condensate elevated (marker of oxidative stress)

• pro-inflammatory cytokines, TNF-α, IL-6, and IL-8 elevated in serum
  • regulatory cytokines, IL-10 decreased
Behavioral and ADHD

• Overlap of symptoms

• Even mild OSA and habitual snoring have been associated with hyperactivity, difficulties concentrating, attention problems and impulsivity

• Tucson Children’s Assessment of Sleep Apnea (TuCASA) study – children with untreated OSA had attention problems and hyperactivity, aggressive behaviours, lower social competencies, poor communication and/or diminished adaptive skills

- *Sleep 2013;36:517-525B.*
Childhood Adenotonsillectomy (CHAT) Study

- the first ever randomized controlled trial to compare adenotonsillectomy with watchful waiting
- primary outcome: change in the attention and executive-function score (Developmental Neuropsychological Assessment)
- adenotonsillectomy resulted in significant improvements in quality of life measures
- however, due to ethical considerations, recruited only mild OSA with no significant oxygen desaturations, above 4 years of age, only followed up for 7 months
- generalizations to other ages and severities of OSA are not possible

CHAT study –
comparison of sleep study and symptoms

- did not undergo adenotonsillectomy
  - 42% had resolution of OSA on follow-up PSG 7 months later (lower apnea-hypopnea index and waist circumference <90% percentile)
  - Only 15% experienced symptomatic resolution (lower sleep questionnaire and snoring scores)

Metabolic morbidities

OSA in adults – well recognized
In children – discrepant findings

Post-pubertal adolescents – strong association between OSA and metabolic syndrome

Pre-pubertal children – lipid and cholesterol alterations and insulin resistance only seen with concurrent obesity

Translational and personalized approaches for pediatric obstructive sleep apnea: ‘Omics’

- why at any level of disease severity, there are children who exhibit morbidity, and those who do not?
- environmental factors: smoking, pollution, diet and levels of physical activity
- genetic factors
  - examples: apolipoprotein E function to explain discrepancies in cognitive function; CRP and IL-6 gene variants in childhood OSA
- epigenetics: occur in OSA and may modify specific aspects of OSA-associated morbidity
  - example: children with high CRP levels exhibited increased methylation of the FOXP3 gene (linear correlation between FOXP3 DNA methylation levels and inflammatory markers)

Adenotonsillectomy

• Outcome or success rate of adenotonsillectomy
  - true percentage? success rate: 75%-80% ???
  - recent study (multicenter retrospective): 30%
    - based on post-op PSG (AHI)

• Complications of T and A (meta-analysis)
  • Children with OSA appear to have more respiratory complications
  • Most frequent early complications are respiratory compromise and secondary hemorrhage

Medical management (pharmacotherapy)

- Tonsillar cultures in OSA: CD3, CD4 and CD8 lymphocytes and proinflammatory cytokines TNFα, IL-1α and IL-6 are increased.
- In vitro experiments: Corticosteroids were added to OSA tonsillar cell cultures, decreased proliferative rates and increased apoptosis, and reduction in the secretion of IL-6, IL-8 and TNFα.
- Randomized crossover trial of intranasal budesonide for mild OSA (6 weeks of therapy):
  - Reduction in OSA severity, decreased adenoidal size.

*Eur Respir J.* 2009;33:1077–84.
*Pediatrics.* 2008;122:e149–55
Leukotriene antagonists (LT)

- **In vitro:**
  - increased levels of leukotriene receptors 1 and 2 in tonsils from OSA
  - LT antagonists to tonsillar cell cultures with dose-dependent reductions in cellular proliferation and secretion of the cytokines TNFα, IL-6 and IL-12

- **Clinically:**
  - recent double-blind placebo-controlled study
    - Improvement in sleep disturbances

*Pediatrics 2012;130: e575–80.*
Risk factors for persistent OSA

• Obesity
• Severe OSA (AHI)>20/hr TST)
• older age (>7 years)
• Asthma
• African ethnicity
• history of prematurity

Prematurity

• often associated with generalized muscle hypotonia
• atypical breathing pattern is associated with the development of mouth breathing and a high and narrow hard palate
• early premature infants often have abnormalities with feeding functions, such as suction, mastication, and swallowing
• weakness of orofacial muscles negatively alter craniofacial growth and lead to a small UA
Special populations
High rate of sleep problems in “special” populations

- basic sleep—wake patterns should form part of routine history-taking
  - especially if child's daytime behavior or mood are suggestive of sleep deprivation
- extended assessment to diagnose and treat the underlying sleep disorder
- treatment decisions need to be based not only on the type of sleep disorder but also, within reason, on the family's preferences and abilities.

Down’s syndrome

• Poor sleep
  - reduced REM sleep and increased slow-wave sleep independent of OSA
  - implications for learning, memory, and behavior
• Anatomy: maxillary hypoplasia and small nose with low nasal bridge midface
• Recurrent upper airway infections → adenotonsillar hypertrophy
• Hypotonia

Craniofacial anomalies

• clinical findings - snoring, work of breathing, desaturations
• congenital craniofacial anomalies is strongly associated with inpatient diagnosis of OSA
• anatomic features - maxillary or mandibular hypoplasia, crowded oropharynx, macroglossia, or poor motor tone

Craniosynostosis

- significant maxillary hypoplasia
- estimated prevalence of OSA of 53% in this population based on symptom report

Apert syndrome  Crouzon syndrome  Pfeiffer syndrome
Oromaxillofacial procedures

- surgical advancement of the midface to enlarge the upper airway
- substantially reduced the AHI and improved oxygen saturation (Pfeiffer, Crouzon, or Apert syndrome and severe OSAS)

Pierre Robin Sequence
Treatment strategies depend on the severity of compromised airways

- Palatal plate with a pharyngeal extension
- Palatal obturator with dorsal extension
- Nasopharyngeal intubation
- Glossopexy
- Mandibular distraction osteogenesis
- Tracheotomy
- Timely and sequential palatal reconstruction

Suction and drinking plate with pharyngeal extension
Pierre Robin sequence surgery

• Tongue-lip adhesion and tongue repositioning can improve apnea/hypopnea index (AHI) and oxygenation saturations

• Systematic review (90 patients)

• tongue-lip adhesion
  ▪ AHI from 30 to 18 events per hour (50% reduction)
  ▪ lowest oxygen saturation from 75% to 84%

• tongue repositioning
  ▪ AHI from 46 to 17 events per hour (62% reduction)
  ▪ mean oxygen saturation from 90 to 95%

Autism spectrum disorder (ASD)

- Sleep problems as high as 80% in children with ASD
- Sleep problems and insufficient sleep →
  - daytime sleepiness, learning problems and behavioral issues
  - hyperactivity, inattentiveness and aggression
- most common sleep problems
  - difficulty falling asleep and repeated awakenings
  - very prolonged awakenings or awaken very early for the day
  - sleep of other family members is often impacted
Poor sleep in ASD

• Neurological
  - abnormalities in brain systems that regulate sleep
  - melatonin and other chemicals released by the brain
• Medical
  - epilepsy or gastroesophageal reflux can disrupt sleep
  - medications taken can be alerting and contribute to difficulty falling asleep
• Psychiatric
  - anxiety and/or depression can interfere with sleep
• Behavioral
  - poor sleep hygiene and limit-setting problems
• Others: sleep apnea, sleepwalking, nightmares, restless legs syndrome
Medical Burden and Age

- Medical burden and severity of sleep disorders increase significantly with age
- Sleep wake symptoms decreased with age (daytime drowsiness, insomnia, fatigue)
- Advancing age may be associated with a decrease in symptom awareness

Markers of OSA
Urinary markers

• morning urinary samples
  - OSA may result in alterations in renal glomerular or tubular permeability (increased catabolism of proteins)
• nocturnal alterations in urinary neurotransmitters
  - episodic hypoxemia and arousals likely result in heightened sympathetic activity, and may be associated with increased levels of urinary catecholamines (epinephrine and norepinephrine)

Data levels

Risk factor/environment

Clinical

Pathophysiological

Biological

Genetic/-omic

Component examples

Risk factor/environment

- Allergens
- Sleep patterns
- Alcohol
- Medications

Clinical

- Cardiovascular disorder
- Age
- Metabolic disorder
- Cancer
- Sex

Pathophysiological

- Muscle responsiveness
- Upper airway anatomy
- Lung volumes
- Ventilatory drive

Biological

- Neurohormonal changes
- Inflammation
- Fibrinolytic imbalance
- Oxidative stress
- Endothelial dysfunction

Genetic/-omic

- Pharmacogenomics
- Epigenetics
- GWA
- miRNA
- Noncoding DNA

Potential clinical relevance [selected examples]

Lifestyle
- Modifiable factors (weight loss)

Clinical phenotypes
- Integrated care
- Risk stratification (EDS, elderly)
- Comprehensive guidelines

Intermediate phenotypes
- Therapeutic targets (oxygen, sedatives)
- Diagnostic (PALM)
- Therapy response (CCC)

Biomarkers
- Diagnostic (IL-6, IL-10)
- Therapeutic targets
- Sequelae predisposition

Genetic risk assessment
- OSA risk
- Sequelae predisposition
- Response to therapy (miRNAs and resistant HTN)
Genomic and proteomic approaches

Pipeline of approaches in diagnosis and personalized treatment of OSA

Different Clinical Faces of OSA

• 822 subjects predominantly middle-aged obese males with severe OSA
• Three distinct clusters:
  (1) “disturbed sleep” cluster (33%)
  • - insomnia-related symptoms
  (2) “minimally symptomatic” cluster (25%)
  • feeling rested on awaking
  (3) “excessive daytime sleepiness” cluster (42%)
  • the presence of daytime sleepiness-related symptoms (such as falling asleep unintentionally during the day, dozing off while driving), and symptoms of witnessed apneas and loud snoring

Will you treat the same?

- Findings and Key points:
  - screening for OSA in those with insomnia
  - treatment with combination therapies (e.g., positive airway pressure and cognitive behavioral therapy for insomnia)
  - comorbid hypertension and cardiovascular disease were highest in the “minimally symptomatic” but lowest in the “excessive daytime sleepiness” group

Am J Respir Crit Care Med. 2015 Nov 1;192(9):1127-9.
Why the “minimally symptomatic” have more co-morbidities?

• Potentially longer lag time between initial symptoms and diagnosis in minimally symptomatic compared with symptomatic patients

• Therefore, longer duration of exposure to untreated OSA
Lessons learned as clinicians

• increase awareness of the heterogeneity of OSA
• guidance as to the differing OSA phenotypic presentations
  - early identification of OSA and lead to the development of
• personalized therapies
  (need for treatment even for less symptomatic or who experience less
common symptoms of OSA)
Current treatment options

• **CPAP**
  - improve daytime sleepiness and quality of life
  - reduce hypertension and cardiovascular events
  - but poorly tolerated (up to 50% of patients unable to tolerate or adhere to therapy beyond 3 months)

• **Mandibular advancement splints (MAS)**
  - 48% and 64% of patients can be effectively treated (reduce AHI to <5 events/h)
  - higher adherence (offsetting the treatment efficacy of CPAP)
Current treatment options (continued)

• Upper airway surgical procedures
  - uvulopalatopharyngoplasty or UPPP
  - nasal surgery, tonsillectomy, various palatal procedures, tongue base reduction and repositioning surgeries, maxillomandibular advancements (MMA), and tracheostomy

• Weight loss
  - lifestyle interventions
  - surgical weight loss
Mechanisms of OSA

Upper airway narrowing
- adenotonsillar hypertrophy
- obesity

Upper airway collapsibility
- decrease in muscle tone: neuromuscular diseases/cerebral palsy
- airway inflammation: rhinitis
- obesity

Airway patency
Non-anatomic factors (or traits)

(1) an oversensitive ventilatory control system (ie, ventilatory control instability or high loop gain)
(2) a low respiratory arousal threshold,
(3) poor pharyngeal muscle responsiveness
High “loop gain”

• Loop gain
  - negative feedback system controlling ventilation
• corrective ventilatory response in relation to ventilatory disturbance

• 1/3 of OSA patients with hypersensitive ventilatory control system
• a large response to a small disturbance is a high “loop gain”
• oscillations in ventilation and ventilatory drive predispose the airway to further collapse
• Possible therapies:
  - oxygen and acetazolamide

Am J Respir Crit Care Med 2004;170: 1225–32.
Low arousal threshold - sedatives

• As pharynx is collapsing, respiratory stimuli can activate the upper airway dilator muscles to restore pharyngeal patency, thus protecting against OSA

• several studies have used sedatives in an attempt to raise the arousal threshold, thereby allowing patients more time to recruit pharyngeal muscles during sleep and achieve stable breathing

• eszopiclone and trazodone
Summary

• Pathophysiology of OSA – mechanics of upper airway narrowing and increased airway collapsibility

• Yet, pediatric OSA spectrum is complex

• Phenotypic variations due to interplay of genetic, environmental, disease severity and individual susceptibility factors

• Is it time to look into personalized treatments for pediatric OSA -precision medicine, for improved outcomes?