Pediatric Sleep Disordered Breathing

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Faculty Disclosure

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- AASM Board of Directors (active)
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Educational Objectives

- Recognize the different sleep-disordered breathing (SDB) patterns in youth
  - List genetic, neurodevelopmental conditions a/w increased risk for SDB
- Discuss diagnostic approaches, current and future
- Describe up-to-date, evidence-based treatments for pediatric SDB
- Identify areas of uncertainty in this field

Common Abbreviations

- AT, adenotonsillectomy; ATH, adenotonsillar hypertrophy
- CHAT, Childhood AdenoTonsillectomy study
- MSDB, mild sleep disordered breathing, aka “primary snoring”
- OSA, obstructive sleep apnea
- oAHI, obstructive apnea hypopnea index
- oSDB, obstructive sleep disordered breathing
- PAP, positive airway pressure
- PSG, polysomnography (sleep and breathing)
- SDB, sleep disordered breathing
Patterns of SDB Inform Treatment

- Pediatric Sleep Disordered Breathing
  - Obstructive oSDB
  - Central Apnea and Hypoventilation
  - Sleep-Related Hypoxemia and/or Hypoventilation Due to Other Disorders

Upper Airway → Brain → Periphery → Lower Respiratory Tract

oSDB
Sleep Apnea in Eight Children

Christian Guilleminault, M.D., Frederic L. Eldridge, M.D., F. Blair Simmons, M.D., and
William C. Dement, M.D.

From the Sleep Disorders Clinic and the Division of Respiratory Medicine and Otolaryngology, Stanford
University School of Medicine, Stanford, California.

Where it all began...

There are not sufficient data to determine exactly where normality ends and pathology begins. Does the occurrence of ten apneic episodes per night indicate that a discrete dysfunction of the central control of respiration exists in these children? Are these children “at risk” for redeveloping a sleep apnea syndrome in adulthood? A careful, long-term follow-up of these and other similar cases may answer these questions.

Thank You Dr. Cathy Hill!

oSDB in Children and Teens

- Prevalent: 10% snore, 1-5% have oSDB (cutpoint?)
  - Higher in obesity and other co-morbid conditions
- Short and long-term complications can be significant
  - a/w neurocognitive impairment, behavioral problems, learning difficulties, mood disturbance, secondary enuresis, cardiovascular and metabolic changes, impaired growth (↓ or ↑), increased health care costs
- Uncertainty: thresholds, vulnerability, natural history
Risk Factors for Childhood oSDB/OSA

- Adenotonsillar hypertrophy
- Adenotonsillar hypertrophy
- Adenotonsillar hypertrophy
- Co-morbid conditions
  - Craniofacial, genetic, neuromuscular, obesity

Factors That Narrow the Airway

Oropharynx most narrowed where adenoids and tonsils overlap

after Ferber R., Solve Your Child’s Sleep Problems, 1985
Multiple Mechanisms for oSDB

- Loop Gain: Oversensitive Ventilatory Control System
- Poor Muscle Response: Gain and Reflex
- Anatomy: Small Collapsible Upper Airway
- Sleep Wake Mechanisms: Arousal Thresholds

Relative role of these traits in pediatric oSDB? vary by age?

Conditions at High Risk for oSDB

- Obesity
- T21
- Prader-Willi
- Skeletal Dysplasia
- Beckwith Weidemann
- Pierre Robin
- Muscle weakness
- Cerebral palsy
- Sickle Cell Disease
- Craniosynostoses
- Spina bifida Chiari I
- Storage Diseases
Other oSDB Risk Factors

• Co-morbidities associated with ↑ risk:
  • Asthma, nasal allergies, sickle cell
  • African-American children: 2-4x risk
  • Perinatal influences (prematurity, 3x risk)
  • Prior adenotonsillectomy
    • Unmasks anatomic or functional mechanisms
  • Positive family history: 2-4x risk
  • Socio-cultural differences
    • ETS, infections, irritants, sleep deprivation, disadvantaged neighborhoods

Differences in Presentation: Child vs. Adult

<table>
<thead>
<tr>
<th></th>
<th>Child</th>
<th>Adult</th>
<th>Obese Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M=F</td>
<td>M&gt;&gt;F</td>
<td>M&gt;&gt;F</td>
</tr>
<tr>
<td>Peak age</td>
<td>2-8 years</td>
<td>Mid-life</td>
<td>Preteen/Teen</td>
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<tr>
<td>Obesity</td>
<td>+</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Chief Complaint</td>
<td>Snore Behavior/Learning</td>
<td>Sleepiness</td>
<td>Snore/EDS Behavior/Learning</td>
</tr>
<tr>
<td>Arousal</td>
<td>±</td>
<td>++++</td>
<td>+ to ++++</td>
</tr>
<tr>
<td>Respiratory pattern</td>
<td>Obstructive hypoventilation</td>
<td>OSA</td>
<td>OH to OSA</td>
</tr>
<tr>
<td>Role for AT</td>
<td>Common</td>
<td>Rare</td>
<td>Yes, but ↑ likelihood of residual OSA</td>
</tr>
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</table>
How Is OSA Diagnosed?

**Peds OSA Consensus Definition (ICSD-3) – place to start**

Criteria A and B must be met

A. The presence of one of more of the following:
   1. Snoring
   2. Labored, paradoxical, or obstructed breathing during sleep
   3. Sleepiness, hyperactivity, behavioral or learning problems

B. PSG demonstrates one or both of the following:
   1. One of more obstructive apneas, mixed apneas, or hypopneas per hour of sleep **OR**
   2. A pattern of obstructive hypoventilation ≥ 25% of TST with CO₂ > 50 mmHg a/w:
      a. Snoring
      b. Flattening of the inspiratory nasal pressure waveform
      c. Paradoxical thoraco-abdominal motion

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**Child vs. Adult Scoring of Respiratory Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive</td>
<td>2 missed breath duration No corroboration required</td>
<td>10 sec duration No corroboration required</td>
</tr>
<tr>
<td>Central</td>
<td>2 missed breath duration Assoc : 3% desat, arousal, or HR &lt;50 for 5 sec* If 20 sec duration, no corroboration needed</td>
<td>10 sec duration</td>
</tr>
<tr>
<td>Hypopnea</td>
<td>≥ 30% 4-NP or back-up Assoc: 3% desat, arousal</td>
<td>10 sec duration ≥ 30% 4-NP + 4% desat or ≥ 30% 4-NP + 3% or arousal</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>≥ 25% TST with CO₂ &gt;50 mmHg EtCO₂ or tcCO₂ or arterial Recommended</td>
<td>↑ CO₂ &gt;55 mmHg for ≥ 10 min ↑ CO₂ &gt; 10 mmHg from wake supine to sleep w/ values &gt;50 mmHg for &gt;10 min Optional</td>
</tr>
</tbody>
</table>

*If age < 1 yr, use <60 bpm for 15 sec*

OSA Diagnosis: PSG Criteria

- Lab-based PSG has been “gold standard”
- Night-to-night reliability is 85-100%
  - PM: moving into “prime time” for pediatric patients?
- Severity rating for oAHI (central apneas typically excluded)
  - Very mild, ≥ 1 to 1.99
  - Mild, ≥ 2 to 4.99
  - Moderate ≥ 5 to 9.99
  - Severe ≥ 10
- Interpretation is not all about AHI: consider SpO₂ (>2% TST < 90% is “a lot”), hypoventilation (>25% TST with CO2 > 50 mmHg), work of breathing, thoracoabdominal asynchrony, sleep fragmentation

Diagnosis of oSDB is Problematic

- Symptoms and physical exam are poor predictors
  - Snoring (“warning sign”) is insufficient to predict oSDB risk
  - 50-65% meet PSG criteria if a/w clinical symptoms and signs
- Diagnosis focuses on PSG as the “gold standard”
  - Limited availability and access, high cost, intensive use of resources, need for specialized techs and physicians to administer and interpret
  - AHI threshold, vulnerability, natural history are uncertain
Other Limitations of oAHI-based Definition

- Relevance to
  - Adolescents
  - Groups with other comorbid conditions
- Other physiologic data may be important
  - Pattern of hypoxemia
  - Sleep fragmentation
- Not a good predictor neurocognitive outcomes, response to therapy

Role of PSG for OSA Dx Varies Stakeholder (US View)

<table>
<thead>
<tr>
<th></th>
<th>ATS¹</th>
<th>AASM²</th>
<th>AAP³</th>
<th>Oto⁴,⁵</th>
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<tbody>
<tr>
<td>Year</td>
<td>1999</td>
<td>2011</td>
<td>2012</td>
<td>2011, 2019 update; AASM editorial</td>
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<tr>
<td>Recommend</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Advocate if,</td>
</tr>
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</table>
| Target         | All  | All   | All  | < 2 yr
|                |      |       |      | • Special groups: obesity, T21, craniofacial, neuromuscular disease, SCD, storage disease |
|                |      |       |      | • Discrepancy between exam and severity of symptoms |

2. Sleep 2011;34:389-398
Other “Diagnostic” Tests

- Clinical symptoms and signs
  - Tonsil size: ☺
  - Video and audio recordings: ±
  - Questionnaires: ± 50/50; PSQ can be helpful
- Lateral neck X-ray: ☺
- Plasma and urinary markers: ?
- Pulse oximetry: ? kids may not desaturate much
- Derived signals from PSG beyond oAH1: ?
- Cardiorespiratory polygraphy aka PM, HSAT: ?

Cardiorespiratory Polygraphy

- Less invasive, more convenient, cost-effective?
- Data quality, need to repeat?
- Acceptable sensitivity and specificity?
- Signal loss and artifacts?
- False negatives in mild oSDB
- Fewer signals needs a more savvy reader

AASM Position Statement: not ready for prime time
JCSM 2017; 13:1199-1203
Management Options (A): Pediatric oSDB

- **Surgical**: 1st line → adenotonsillectomy
  - 80% effective (depends on cut point, 50 to 100%)
  - Tracheostomy or targeted surgeries (for craniofacial disorders)
  - Hypoglossal nerve stimulators (trial in T21)
- **Medical therapies**
  - CPAP, especially if moderate to severe residual OSA
    - High flow cannulas?
  - Anti-inflammatories (nasal steroid, montelukast) for mild residual OSA
  - Supplemental oxygen (now mentioned in ATS statement)
- **Watchful waiting/supportive care** (from CHAT experience)

Management Options (B): Pediatric oSDB

- Dental: rapid maxillary expansion; MAD; only selected patients
- Positional therapy
- Weight loss (always recommended, difficult to achieve)
- Myofunctional therapy: highly marketed; who benefits most?
PAP: Compliance, Complications, Outcomes

- Use in a wide age range, often multiple co-morbidities
- Symptoms improve, safe, effective, improved health outcomes
- Labor intensive, > 20% drop out
  - Immediate acceptance: only half
  - Delayed acceptance over a year; 80% in 3 mo
  - School age > teens > toddler/preschool
  - Full face mask harder to accept
  - Worse adherence not predicted by ↑ comorbidities
- Compliance varies, need objective monitoring
- Complications rare (leak, skin breakdown)
- Need to monitor craniofacial growth

Game Changers for oSDB

Newer data that may change practice and challenge role of PSG data in management
ChildHood AdenoTonsillectomy (CHAT) Study

• NIH-funded, multi-site, randomized, single-blinded controlled trial of early adenotonsillectomy (eAT) vs watchful waiting for OSA (oAHI, 2 to 30, w/o desat*)
  – Ages: 5-9 y, otherwise healthy, snoring, ATH, and ATx candidates
  – 50% M, 50% overweight, 61% minority, median oAHI ~ 5
  – Assessed at baseline and 7 m later
• Aims: determine effect of eAT on 1) attention/executive and cognitive function; 2) symptoms PSG, and quality of life
• Identify factors that moderate response to ATx surgery
  – Race, obesity, OSA severity by oAHI, age

CHAT Outcomes: eAT vs Watchful Waiting (n~ 400)

• No significant group differences in the primary outcome, measured executive functioning
• Significant parent-reported improvements after AT:
  • Global behaviors, including executive functioning, attention
  • Generic and disease specific quality of life
  • OSA symptoms, snoring and sleepiness
• Normalization of PSG in a larger proportion of the early AT vs watchful waiting (79% vs 46%)

* ≥ 2% of TST with SpO2 < 90%

Normalization of PSG
Less likely if AA, obese, higher AHI


Other Findings From CHAT That May Change Your Thinking about oSDB
Do Clinical Parameters Predict OSA Severity by PSG?

Not Much 😁

- In screening sample (n~1200), only AA race and environmental tobacco smoke were associated with 20% higher AHI.
- In study sample (n~450), gender, tonsillar size, palate position were not predictors of OSA severity based on PSG variables.
  - Race, BMI z > 2, symptom scales (PSQ, OSA-18) a/w higher oAHI or ODI
  - Clinical variables explained only ~ 3% of variance in OSA severity


How Did Growth Change After AT?

Watch Out!

Significantly greater weight gain 7 mo after AT in all categories (FTT, normal, overweight, obese)
- AT normalizes weight in children with FTT
- ↑ risk for obesity in overweight children (eAT vs. WW; 52% vs 21%)

Need for pro-active monitoring weight, nutritional counseling, and encouragement of physical activity

What About Parent-Ratings of Symptoms, QOL?
Big!

- eAT compared with WW resulted in more improvements in generic and OSA-specific QOL measures and OSA symptoms
  - Effect sizes for improvement in QOL: moderate/large
  - Effect modification: race, but not AHI, obesity
  - Improvement in OSA by PSG accounted for only a small portion of the variance in QOL

Utility of Symptoms (vs AHI) to Predict Treatment Outcomes in OSA?
Yes, better than PSG

- PSQ symptom inventory better predicted key AT-responsive OSA comorbidities (executive function, behavior, quality of life, and sleepiness) and their improvement after eAT
- In contrast, baseline PSG data did not independently predict these morbidities or their post-op improvement.
Predictors of Spontaneous OSA Resolution?

- 42 – 48% of patients will have an OSA resolution by PSG, but…
  - Only 15% of symptomatic children will resolve symptoms
- More PSG-related OSA resolution if mild OSA at baseline
- 23% of habitual snorers stopped snoring
- Spontaneous resolution maybe more likely with less central adiposity

Utility of PSG Thresholds in OSA Management

- Re-analysis of CHAT data: 18 health outcomes changes, given resolution of OSA or change in severity by PSG
- PSG resolution and change in PSG severity accounted for a small, but significant proportion of changes in symptoms (PSQ-SRBD) and disease-specific QOL (OSA-18)
- No PSG mediation for remaining 16 outcomes (cognitive, behavioral, generic QOL, or other health).
Value Added of EtCO\(_2\) Data? **Not Much**

- 91% of screening PSGs had quality waveforms ≥ 75% time
- Hypoventilation criteria met: 5% screened; 17% randomized
- TST with EtCO\(_2\) > 50 mmHg
  - Modest correlations with oAH1 and SpO\(_2\) ≤ 92%
  - Greater decrease after eAT vs WW, higher values in AA children
  - Did not predict post-op changes in cognitive or behavioral measures

Heads Up: oSBD Studies in Progress

- PATS: RCT of eAT vs WW for oSDB (snore to oAH1 < 3) in 3 to 12 yr
- POSTA: RCT of eAT vs WW for oSDB (snore to oAH1 < 10) in 3-5 yr
- HELP-DS: observational feasibility study in Down syndrome having AT

Role of full in lab-PSG in diagnosis and management of routine SDB in the future?
Central apnea and hypoventilation

Conditions at High Risk for Central Apnea and/or Hypoventilation

- Spina bifida
- Prader-Willi
- Achondroplasia
- Mitochondrial Disorders
- Rett Syndrome
- Muscle weakness
- Cerebral palsy
- CCHS
- Chiari I
- Familial Dysautonomia
- Morbid Obesity
Central Apnea in Childhood

- Central sleep apnea in early infancy is usually part of immaturity of respiratory control
- Outside of infancy (and altitude), central sleep apnea, with or without hypoventilation is a very unusual respiratory pattern in a child and usual requires further evaluation!
- If the child is otherwise normal, suspect hindbrain malformation such as a Chiari I malformation.
- Other disorders: neurodevelopmental, metabolic or genetic

If > 1 y/o, typically developing and central apnea index ≥ 5, then think more.

Congenital Central Hypoventilation Syndrome

- Rare disorder of autonomic dysregulation
- Profound hypoventilation; NREM > REM > ± Wake; ⊗ CO₂ response, ↓ O₂ response
- Normal respiratory rate, ↓ tidal volume rather than central apnea
- Hirschsprung’s ~20%, neural crest tumors ~6%, other ANS dysfunction
- PHOX2B, disease-defining gene, must test patient, parent
- Autosomal dominant, heterozygote, 90% de novo
  - 90% from polyalanine repeat expansion, 10% other
  - PHOX2B genotype informs CCHS phenotype
  - If PHOX2B is negative, look for another disease

CCHS: Not Just for Babies

- Can present in later infancy, child- or adulthood
- Late-onset CCHS (LO-CCHS)
  - Variable penetrant (20/24, 20/25 or rarely NPARM)
  - Clinical pearl – consider LO-CCHS if central alveolar hypoventilation, cyanosis, or seizures after
    - Administration of anesthetics or CNS depressants
    - Recent severe pulmonary infection
    - Treatment of OSA
- PHOX2B testing required, patient and parent!

ROHHAD: Late Onset Central Hypoventilation

- Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation
- Endocrine dysfunction: ↓ thyroid, ↓ GH, DI, precocious puberty; temperature instability
- Association with tumors of neural origin
- Rapid weight gain with hyperphagia between 3 to 10 y
- High incidence of respiratory arrest, 50-60% require ventilation
- PHOX2B mutations not seen
Other medical conditions a/w SDB and worthy of special mention

Trisomy 21 (Down Syndrome)
Extra 21st chromosome; 1/800 live births

- OSA prevalence
  - children (30-55%)
  - Adults 88% moderate (>15), 69% severe (>30)
- OSA risk: hypotonia, large tongue, midface hypoplasia, tendency toward obesity; ↑ risk with hypothyroidism
- Poor correlation between report and PSG results
  - AAP recommends PSG by age 4 yr

Pediatrics 2011; 128:393-406
Prader-Willi and Pediatric SDB
Partial deletion of 15q, usually paternal; 1 in 10-25K

- OSA a/w ↑ obesity; risk for obesity hypoventilation syndrome
- Blunted ventilatory and arousal responses to O₂
- Shifted CO₂ set point, ↓ response to CO₂ after obesity
- Narcoleptoid* features in 20%
- Treatment with hGH which can worsen OSA and CSA

Features: hypotonia, short stature, hyperphagia, obesity, behavioral problems, intellectual disability, small hands and feet, unusual facies

Achondroplasia, other forms of dwarfism

- SDB risk factors for both OSA (10-87%) and central apnea:
  - Midface retrusion, short cranial base, obesity
  - Brainstem compression @ foramen magnum,
  - Pulmonary restriction
- Monitoring for OSA at all ages is part of AAP Health Supervision
Obesity Hypoventilation* in Children:
Impaired central chemoreceptor response (primary or secondary?)

Associated conditions:
• Prader-Willi
• ROHHAD
• Exogenous obesity with UAO
• Trisomy 21

*AKA “Pickwickian syndrome”

Spina Bifida
Chiari II malformation, VP shunt, spinal cord defect

• Respiratory control abnormalities
  • Apnea, bradypnea, hypoventilation
  • Absent O₂, CO₂ responses
  • OSA 2º vocal cord paresis
  • Breath-holding spells
• Restrictive lung disease
Chiari I Findings

- Herniation of cerebellum or brainstem into foramen magnum
- Presents @ any age with central sleep apnea, OSA, and/or hypoventilation
- Other symptoms: H/A, neck pain, ataxia, syncope, oculomotor or NONE
- Neurosurgery may help; can recur
- If residual central sleep apnea and/or hypoventilation, support needed

Wrap Up and Time for Questions
Challenges: Today and Future

- Current best practices, scoring rules: mostly based on consensus and expert opinion
- New data from active pediatric studies will change our beliefs and practices
- Predicted practice changes
  - AHI cannot be our primary outcome, not a good predictor for outcomes we care about
  - Home CR studies will play a greater role in routine oSDB decision making
  - Human PSG scoring will be replaced by machines
  - Personalized medicine/endotyping: which child most likely to benefit from XYZ?
    - Most of your patients will not be typically developing or will have significant comorbid conditions
  - Telemedicine, wearables and nearables, Walmart and CVS will be part of Team Sleep

Thank You!

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