Apnea of Prematurity and hypoxemia episodes

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Objectives

• Differentiating between apnea and hypoxemia episodes.
• Pathophysiology
• Diagnosis of apnea and work up
• Treatment strategies and controversies
• Hypoxemia episodes in ventilated infants
• Treatment strategies

Apnea Definition and Pitfalls

• Developmental disorder occurring in infants born before 34wk of gestation.
• 80% of ELBW infants.
• Respiratory pause for 15-20seconds, or accompanied by bradycardia or hypoxemia.
• Problems:
  – Definition dates back to 1969.
  – Not really valid with current monitoring in NICU
  – Not valid for infants receiving mechanical ventilation

Intermittent Hypoxemia Episodes (Desaturations)

• Common end point resulting in adverse long term outcomes.
• Easily detected and monitored.
• No consensus definition on duration and degree
• Management depends on underlying cause of hypoxemia:
  – Apnea
  – Hypoventilation

Pathophysiology of Apnea

[Diagram showing the relationship between immaturity, enhanced inhibitory reflexes, diminished hypercapnic responses, hypoxic depression, and apnea.]

[Graph showing the difference in slopes between infants with and without apnea.]
Types of Apnea

- **Central Apnea:**
  - No inspiratory effort
- **Obstructive Apnea**
  - Chest wall motion without nasal airflow
- **Mixed Apnea**
  - Most commonly observed
  - Obstructed inspiratory effort and central pauses.

Diagnostic Dilemmas

- **Apnea:**
  - Respiratory inductance plethysmography
  - Pneumotachograph
- **Pulse oximetry**
  - Noninvasive, continuous, instant results
  - Not accurate at levels below 60-70%
  - Ideal normal range not known
  - Signal loss and false alarms

MANAGEMENT OF APNEA OF PREMATURITY

Differential Diagnosis

- **Seizures**
- **Hypoxemia or Anemia**
- **Infection**
- **Drug Therapy**

Lab evaluation

- **CBC:** Anemia and Sepsis
- **Blood culture:** Sepsis
- **Blood glucose:** hypoglycemia
- **Blood gas:** hypoxemia and acidosis reflecting sepsis or NEC
- **Cranial imaging**
Treatment options for Apnea of Prematurity

<table>
<thead>
<tr>
<th>Intervention with proven benefit</th>
<th>Interventions requiring further study</th>
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<td>Positive Airway Pressure:</td>
<td>Body Positioning</td>
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<tr>
<td>- Nasal CPAP</td>
<td>Sensory Stimulation</td>
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<tr>
<td>- NIPPV</td>
<td>- Kinesthetic</td>
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<tr>
<td>- High flow nasal cannula Oxygen</td>
<td>- Skin to skin</td>
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<tr>
<td>- Mechanical Ventilation</td>
<td>- Olfactory</td>
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<tr>
<td>Methylxanthines:</td>
<td>Improved oxygen carrying capacity:</td>
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<td>- Caffeine</td>
<td>- Oxygen Supplementation</td>
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<td>- Aminophylline</td>
<td>- Red blood cell transfusion</td>
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<td>Nutritional supplementation:</td>
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<tr>
<td>- L-Carnitine</td>
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<tr>
<td>- Creatine</td>
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<td>Anti-Reflux medication</td>
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CPAP

- Mostly effective on obstructive and mixed apnea with minimal effect on central apnea
- Mechanism:
  - Splinting of upper airway
  - Stabilization of chest wall
  - Increase in functional residual capacity

NCPAP or NIPPV

<table>
<thead>
<tr>
<th>Table 1: N-PPV versus N-CPAP in apnea</th>
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<tbody>
<tr>
<td>Population</td>
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<td>Ryan 1989</td>
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<td>Lin 1998</td>
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<td>Sugaig 2007</td>
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Apnea frequency in brackets: N-CPAP, nasal continuous positive airway pressure; N-PPV, nasal intermittent positive pressure ventilation.

CPAP or Caffeine

- 1977: First use for Apnea of prematurity.
- Licensed for short term use for apnea of prematurity in 28-33wk GA.
- One of the most commonly used drug in neonates
- Effects:
  - Physiologic:
    - Increased minute ventilation
    - Shift of CO2 response curve to left
    - Greater efficiency of diaphragmatic contraction
    - Improved pulmonary mechanics
    - Decreased hypoxic ventilatory depression
  - Biochemical:
    - Adenosine receptor antagonism

CPAP or Nasal Cannula

- Problems with CPAP:
  - Nasal irritation, deformity, agitation, nursing care unfriendly
- High flow nasal cannula:
  - More convenient
  - No measurement of pressure generated
  - No studies so far comparing CPAP vs Nasal Cannula

Caffeine

- Licensed for short term use for apnea of prematurity in 28-33wk GA.
Caffeine therapy

- Recent Cochrane review showed that both theophylline and caffeine are effective in reducing apnea in 2-7 days after starting treatment.
- Advantages of Caffeine:
  - Lower toxicity
  - Penetrates CSF better than theophylline
  - Has plasma half life of 100 hr

CAP Trial

- Multicentric RCT comparing caffeine with placebo in infants with apnea of prematurity for neurologic side effects:
  - Less BPD in infants with caffeine
  - Less weight gain for first 3 weeks
  - Improved neurologic outcomes at 18th but no significant effect at 5yr follow up.
  - Did not include infants on ventilator for prolonged period of time

Adverse effects of Caffeine

- Tachycardia
- Poor weight gain
- Irritability
- Seizures
- Necrotizing enterocolitis

CONTROVERSIES IN CAFFEINE TREATMENT

When to start Caffeine

- Early vs Late Caffeine:
  - Retrospective study of 5000 preterm infants showed reduction in BPD, death and PDA treatment.
  - Randomized controlled trial in intubating patients for early vs late caffeine treatment currently underway.

Dose of Caffeine

- Most places in US use 20mg/kg bolus and 5-8mg/kg maintenance dose.
- Most places don’t check level.
- Some studies evaluating dose of caffeine and effect.
Duration of Caffeine therapy

- Depends on half life of caffeine and therapeutic level of caffeine.
- Most places wait for 7 days.
- A prospective study of 48 preterm infants showed that 68% of infants had abnormal sleep study and mean caffeine levels above therapeutic range at 7 days after discontinuation of caffeine.

Monitoring after stopping caffeine

When to discharge after apnea

- Spontaneous episodes different from apnea:
  - Pathophysiology
  - Management
- Increases with increased gestational age and chronic ventilator dependency.
- More common during awake or indeterminate sleep.

Hypoxemia episodes in ventilated infants

Mechanism of hypoxemia episode in ventilated infants

- Forced expiratory effort
- Loss of end expiratory volume
- Reduced lung compliance and increased resistance
- Decreased tidal volume due to constant PIP
- Alveolar hypoxia leading to intrapulmonary shunting

Hypoventilation and Hypoxemia
Management

- Triggered by change in lung volume and ventilation so many times result in higher level of support.
- Avoidance of ventilator patient asynchrony.
- Volume targeted ventilation:
  - Automatic increase in PIP during hypoventilation may lead to earlier restoration of tidal volume and

Volume Guarantee Study

- Randomized crossover study of 24 hr each study period, VG and CV, applied in random sequence.
- Infants with frequent hypoxemia episodes
- Continuous monitoring of SpO2, ventilator parameters with all the routine care procedure continued.

Results

- Decreased the duration of all hypoxemia episodes (SpO2 < 85%)
- Did not reduce the time spent in severe hypoxemia, frequency or duration of severe hypoxemia episodes (SpO2 < 75%)
- Was associated with a reduction in FiO2

Supplemental Oxygen

- Transient increase in FiO2 during the episode:
  - Frequently excessive leading to hyperoxemia
  - High basal level of SpO2 to attenuate these episodes.
  - Dependent on nurse patient ratio
- Automatic FiO2 Control:
  - More effective in maintaining target SpO2 range
  - Does not prevent these episodes.

Consequences of hypoxemia episodes

- Changes in brain oxygenation:
  - Hypoxia, reoxygenation injury
- Long term neurologic effects:
  - Not clearly defined
  - Some mild motor delay and lower MDI reported in infants with more apnea and hypoxemia spells
  - Difficult to establish cause and effect relationship
Consequences of hypoxemia episodes

- Retinopathy of prematurity:
  - In animal models, intermittent hypoxia linked to abnormal retinal vascular development
  - Severe ROP in preterm infants had been associated with frequent hypoxemia episodes.

- Lung development:
  - In animal models, associated with abnormal alveolar and vascular development, impaired pulmonary antioxidant defense and surfactant production.