

Causes and management of apnea in the newborn

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Considerations

- Apnea is a common problem in preterm infants that may be due to an underlying illness or to idiopathic apnea of prematurity.
- In term infants, apnea is always worrisome and demands immediate diagnostic evaluation.
- Prolonged apneic events must be distinguished from periodic breathing because they might indicate serious illnesses.
- Apnea is a feature of many primary diseases that affect neonates. These disorders produce apnea by direct depression of the central nervous system's control of respiration (e.g., hypoglycemia, meningitis, drugs, hemorrhage, seizures), disturbances in oxygen delivery (shock, sepsis, anemia), or ventilation defects (pneumonia, RDS, persistent pulmonary hypertension of the newborn [PPHN], muscle weakness).

Potential Causes of Neonatal Apnea and Bradycardia

- **Central nervous system**

Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), and effect of general anesthesia.

- **Respiratory**

Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity (<1,000 g), laryngeal reflex, phrenic nerve paralysis, severe hyaline membrane disease, pneumothorax, hypoxia, malformations of the chest.

- **Infectious**

Sepsis, necrotizing enterocolitis, meningitis (bacterial, fungal, viral), respiratory syncytial virus.

- **Gastrointestinal**

Oral feeding, bowel movement, esophagitis, intestinal perforation, GERD.

- **Metabolic**

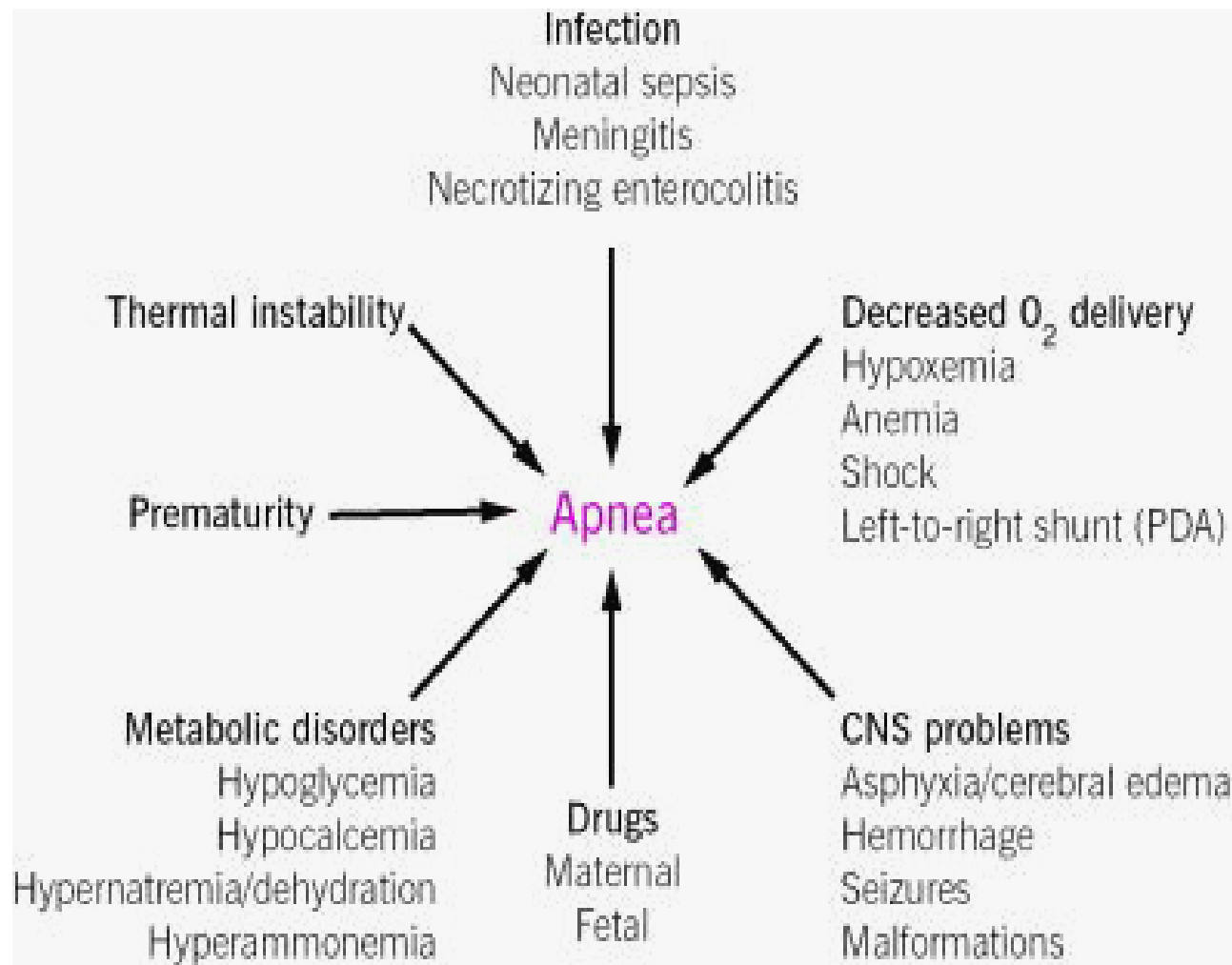
↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↓ organic acids, ↑ ambient temperature, hypothermia.

- **Cardiovascular**

Hypotension, hypertension, heart failure, PDA, anemia, hypovolemia, vagal tone.

- **Other**

Immaturity of respiratory center, sleep state, maternal drugs



Idiopathic apnea of prematurity

Idiopathic apnea of prematurity occurs in the absence of identifiable predisposing diseases.

Apnea is a disorder of respiratory control and may be obstructive, central, or mixed.

- **Obstructive apnea** (pharyngeal instability, neck flexion, nasal occlusion) is characterized by absent airflow but persistent chest wall motion. Pharyngeal collapse may follow the negative airway pressures generated during inspiration, or it may result from incoordination of the tongue and other upper airway muscles involved in maintaining airway patency.
- **Central apnea** is caused by decreased central nervous system (CNS) stimuli to respiratory muscles, airflow; chest wall motion are absent. Gestational age is the most important determinant of respiratory control, with the frequency of apnea being inversely related to gestational age. The immaturity of the brainstem respiratory centers is manifested by an attenuated response to carbon dioxide and a paradoxical response to hypoxia that results in apnea rather than hyperventilation.
- **Mixed apnea** (the most common pattern of in preterm neonates) has a mixed etiology (50–75%), with obstructive apnea preceding (usually) or following central apnea.
Short episodes of apnea are usually central, whereas prolonged ones are often mixed.

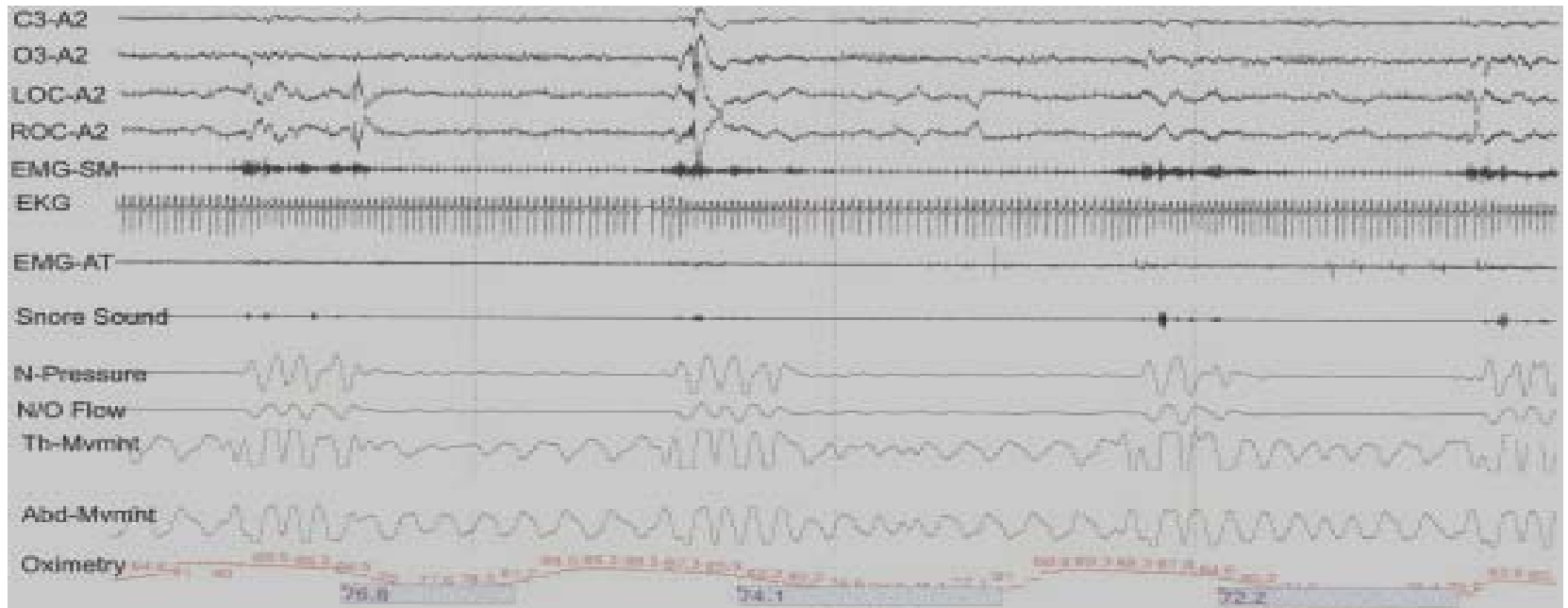
Apnea of prematurity

Incidence:

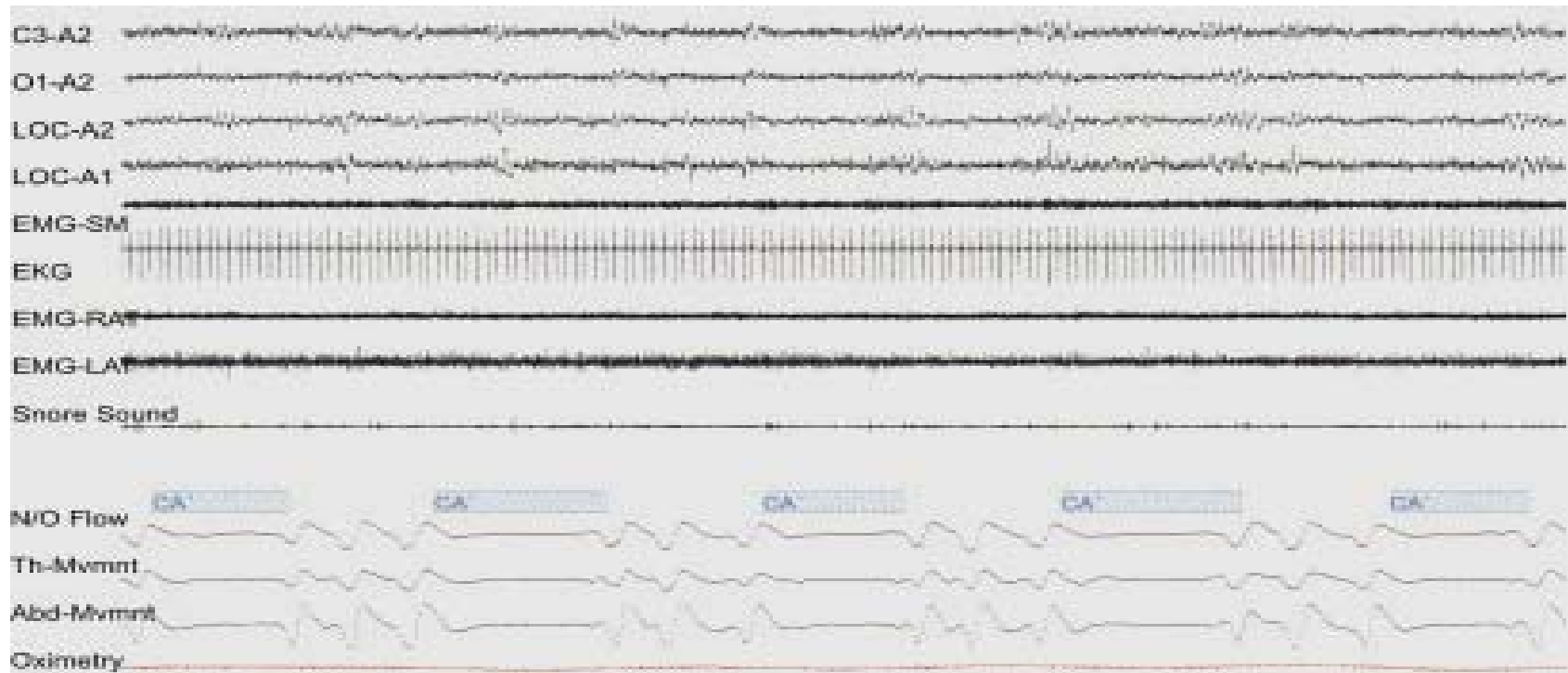
- Apnea occurs in most infants born at <28 weeks gestation, about 50% of infants born at 30 to 32 weeks gestation, and <7% of infants born at 34 to 35 weeks gestation. It usually resolves by 34 to 36 weeks postconceptual age, but may persist after term in infants born at >25 weeks gestation.

Sleep states:

- Apnea is dependent on sleep state; the frequency of AOP increases during active (rapid eye movement) sleep.
- Paradoxical chest wall movements (inspiratory abdominal expansion and inward chest wall movements) are common during active sleep and may cause a fall in Pao₂ because of ventilation-perfusion mismatch.
- Furthermore, increased negative pressure during paradoxical breathing and inhibition of pharyngeal muscle tone during active sleep may contribute to upper airway collapse and obstructive apnea.



Obstructive sleep apnea. This 2-minute segment of an overnight sleep study shows a sequence of four consecutive episodes of obstructive sleep apnea. Note the cessation of breathing revealed by nasal pressure (N-Pressure) and nasal/oral airflow (N/O flow) channels notwithstanding continued respiratory effort shown by thoracic movement (Th-Mvmnt) and abdominal movement (Abd-Mvmnt). Blood oxygen saturation (Oximetry) dips as low as 72.2% in response to the third event depicted. Sleep disturbance (arousal) can be observed following each apnea episode and coincident with resumption of breathing on the top five recording channels: central (C2-A2) and occipital (O3-A2) electroencephalogram; left and right eye electro-oculogram (left outer canthus [LOC-A2] and right outer cantus [ROC-A2]); and chin electromyogram (electromyogram-submentalis [EMG-SM]). Snoring sounds (probably from choking, gasping, or an explosive breath) accompany resumption of breathing. Also shown are channels for electrocardiogram (EKG) and leg movements (electromyogram-anterior tibialis [EMG-AT]).



Central sleep apnea. This 2-minute segment of an overnight sleep study shows a sequence of five consecutive episodes of central sleep apnea. Note the cessation of breathing revealed by nasal/oral airflow (N/O flow) channels coincident with pauses in respiratory effort shown by thoracic movement (Th-Mvmnt) and abdominal movement (Abd-Mvmnt). Blood oxygen saturation (Oximetry) fluctuates only slightly in response to the apnea episodes. In contrast to obstructive events, these central apnea episodes do not routinely terminate with a sleep disturbance (arousal), as can be seen on the top five recording channels: central (C2-A2) and occipital (O3-A2) electroencephalogram; left and right eye electro-oculogram (left outer canthus [LOC-A2] and right outer cantus [ROC-A2]); and chin electromyogram (electromyogram-submentalis [EMG-SM]). No resumption of breathing-related snoring sounds are noted. Also shown are channels for electrocardiogram (EKG) and right and left leg movements (electromyogram-right anterior tibialis [EMG-RAT] and electromyogram-left anterior tibialis [EMG-LAT]).

Clinical Manifestations

- The incidence of idiopathic apnea of prematurity is inversely proportional to gestational age.
- Preterm infants rarely have AOP on the 1st day of life. Apnea immediately after birth suggests of another illness.
- The onset of idiopathic apnea occurs on the 2nd-7th day of life.
- The onset of apnea in a previously well premature neonate after the 2nd week of life or in a term infant at any time is a critical event that warrants immediate investigation.
- In preterm infants, serious apnea is defined as cessation of breathing for longer than 20 sec, or any duration if accompanied by cyanosis and sinus bradycardia.
- The incidence of associated bradycardia increases with the length of the preceding apnea and correlates with the severity of hypoxia.
- Short apnea episodes (10 sec) are rarely associated with bradycardia, whereas longer ones (>20 sec) have a higher incidence of bradycardia.
- Bradycardia follows the apnea by 1–2 sec in more than 95% of cases.
- Vagal responses and, rarely, heart block are causes of bradycardia without apnea.

Treatment

- Infants at risk for apnea should be monitored with apnea monitors.
- Gentle cutaneous stimulation is often adequate therapy for neonatal infants with mild and intermittent episodes.
- Infants with recurrent and prolonged apnea require immediate bag and mask ventilation. Oxygen should be administered judiciously to treat hypoxia.
- Recurrent apnea of prematurity not due to a precipitating identifiable cause may be treated with theophylline or caffeine.
- Methylxanthines enhance ventilation through a central mechanism or by improving diaphragmatic strength. Loading doses of 4 mg/kg of theophylline (orally) or aminophylline (intravenously) should be followed by doses of 2 mg/kg given every 8-12 hr by the oral or intravenous routes.
- Loading doses of 10 mg/kg of caffeine base PO or 20 mg/kg caffeine citrate IV are followed 24 hr later by maintenance doses of 2.5-5 mg/kg/24 hr qd orally (base) or 5-10 mg/kg/day caffeine citrate IV .
- These doses should be monitored by observation of vital signs, clinical response, and serum drug levels (therapeutic levels (through): theophylline, 7-12 µg/mL; caffeine, 8–25 µg/mL).

Treatment (cont)

- Transfusion of packed red blood cells to reduce the incidence of idiopathic apnea is reserved for severely anemic infants.
- The role of gastroesophageal reflux in apnea of prematurity is controversial. Data do not support the use of antireflux medications to reduce the frequency of apnea in preterm infants if there is no symptoms of GERD.
- Nasal continuous positive airway pressure (CPAP, 4–6 cm H₂O) and high-flow nasal cannula (1–2.5 L/min) are effective therapies for mixed or obstructive apnea. Continuous positive pressure splints the upper airway and thereby prevents obstruction.
- When apnea is due to a precipitating illness, airway stability (intubation) and oxygenation must be maintained in addition to therapy for the underlying disease.

Prognosis

- Apnea of prematurity does not alter an infant's prognosis (unless severe, recurrent, and refractory to therapy). Associated problems, i.e. intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity are essential in determining the prognosis of apneic infants.
- Apnea of prematurity usually resolves by 36 wk postconceptional age (gestational age at birth plus postnatal age) and does not predict future episodes of sudden infant death syndrome. Some infants with apnea of prematurity are discharged as long as cardiorespiratory monitoring can be performed at home (with or without medications). In the absence of significant events, home monitoring can be safely discontinued at 44–45 wk postconceptional age.

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Question 1

- You are called to the normal nursery to evaluate a full term male infant, born 2 hours ago by repeat C/S to a 24 y o G2P2Ab0 mother who was GBS positive and not pretreated (no ROM), smoking ½ ppd. Apgar scores were 9/9. The mother plans on breast feeding. The child was noted to be apneic and pale. The pulse ox was 85% and he is now receiving blow-by oxygen.
- *Describe your differential diagnoses and your plan of treatment*

Question 2

You are called to the NICU to evaluate a 6 days old female former 31 weeks of gestation with resolving RDS, who was weaned to RA yesterday, on advancing feeds who has experienced several episodes of apnea and bradycardia today. This is a new finding for this baby.

What would be your approach, differential diagnoses and plan?

Question 3

How would you differentiate obstructive apneas from central apneas?

How would you treat them?

Question 4

You decide to start a 1,500 gm infant on methylxanthines for apnea of prematurity. Please calculate the loading dose and the maintenance dose and state the dosing interval if you choose to use:

	Loading dose	Maintenance Dose	Dosing interval
Theophylline IV			
Theophylline PO			
Caffeine IV			
Caffeine PO			

Question 5

What criteria would you use to discontinue the home apnea monitor on:

- *A 5 weeks old, former 32 weeker, discharged 10 days ago?*
- *A 16 weeks old, former 25 weeker, discharged from the NICU 10 days ago?*
- *A 2 weeks old full term infant who's sibling died of SIDS?*