16 Apnea

About 30-45% of preterm neonates exhibit periodic breathing pattern characterized by three or more respiratory pauses of greater than 3 seconds duration. Periodic breathing is a normal event in preterm infants, reflective of immaturity of respiratory control system and does not merit any treatment. In contrast, apnea is a pathological cessation of breathing that results in hemodynamic disturbances and merits treatment.

Definition

Apnea is defined as cessation of breathing for longer than 20 sec, or for shorter duration in presence of bradycardia or change in skin color (pallor or cyanosis).[1] Significant bradycardia has been defined as heart rate <80 bpm and significant desaturation defined as oxygen saturation <80-85%.[2]

Incidence

Apnea is usually related to immaturity of the respiratory control system in preterm infants and called as apnea of prematurity (AoP). Apnea can also be a manifestation of many other diseases in neonates.

The incidence of AoP is inversely proportional to gestational age. It varies from 10% in infants born at gestation of 34 weeks or more to more than 60% in infants born at less than 28 weeks of gestation.

Etiology of apnea[3,4]

Apnea of prematurity(AoP)

It is related to immaturity of the brainstem and peripheral chemoreceptors resulting in abnormal ventilator response to hypercarbia and hypoxia, along with immature reflex responses. . This condition usually presents after 1-2 days of life (detection may be delayed by the presence of ventilatory support in the initial few days of life) and within the first 7 days.

Apnea occurring in first 24 hours and beyond 7 days of life is more likely to have a secondary cause than being AoP.

Secondary causes

Secondary causes of apnea include:

a) **Temperature instability:** hypothermia and hyperthermia, especially frequent fluctuations in body temperature
b) **Metabolic:** acidosis, hypoglycemia, hypocalcemia, hyponatremia, hypernatremia
c) **Hematological:** anemia, polycythemia
d) **Neurological:** intracranial infections, intracranial hemorrhage, seizures, perinatal asphyxia, and placental transfer of drugs such as narcotics, magnesium sulphate, or general anesthetics
e) **Pulmonary:** respiratory distress syndrome (RDS), pneumonia, pulmonary hemorrhage, obstructive airway lesion, pneumothorax, hypoxemia, hypercarbia, airway obstruction due to neck flexion
f) **Cardiac:** congenital heart disease, hypo/hypertension, congestive heart failure, patent ductus arteriosus
g) **Gastro-intestinal:** gastro esophageal reflux, abdominal distension, NEC
h) **Infections:** sepsis, pneumonia, meningitis, necrotizing enterocolitis

AoP is a diagnosis of exclusion. It should be considered after the secondary causes have been excluded. Common causes of secondary apnea include temperature instability, airway obstruction, metabolic causes such as hypoglycemia and hypocalcemia, respiratory distress syndrome, sepsis, polycythemia and anemia.

Types of apnea[5]

a) **Central apnea (40%):** Central apnea is characterized by cessation of inspiratory efforts due to reduced central drive.
b) **Obstructive apnea (10%):** In obstructive apnea, the infant is not able to breathe due to obstructed airway. In this type of apnea, there is chest wall motion without any airflow.

c) Mixed apnea (50%): has both components- reduced central drive followed by obstructed airway.

The source of obstruction in preterm neonates is generally abnormal neck position (undue flexion or extension) and/ or secretions. Other sources of obstruction are uncommon.

Monitoring

All neonates less than 35 weeks gestation should be monitored for apnea in the first week of life.

Management

Emergency treatment

The neonate should be checked for bradycardia, cyanosis and airway obstruction. The neck should be kept slightly extended. The airway should be suctioned if secretions are present. Most apneic spells respond to tactile stimulation. Oxygen by head box or nasal cannula is provided if the infant is hypoxic. If the neonate does not respond to tactile stimulation, positive pressure ventilation (PPV) should be initiated.

Clinical examination

After stabilization, the neonate should be evaluated for possible underlying cause. History should be reviewed for secondary causes such as perinatal asphyxia, maternal drugs, neonatal sepsis and feed intolerance. He should be examined for temperature instability, hypotension, pallor, cardiac murmur for PDA and poor perfusion.

Investigations

Affected neonates should be subjected to following investigations, *on an individualized basis*, to exclude common secondary causes of apnea: blood glucose, hematocrit, electrolytes, sepsis work up, chest x-ray, ultrasound head and other investigations depending on the history and physical examination (Table 16.1).

Table 16.1: Investigations to rule out secondary causes of apnea

Suspected cause for apnea	Clinical features	Investigations
Sepsis, pneumonia, meningitis	Lethargy, decreased feeding, fast breathing, retraction, brady/ tachycardia, shock	Sepsis work-up chest X-ray
Patent ductus arteriosus	Tachycardia, bounding pulses, hyperkinetic precordium, cardiac murmur, increased requirement for respiratory support	Chest X-ray, echocardiography
Periventricular-intraventricular hemorrhage	Sudden onset of pallor, shock, deranged sensorium	Cranial ultrasonography
Metabolic: hypoglycemia, hypocalcemia, hyponatremia	Jitteriness, poor feeding, seizures	Measurement of blood sugar, calcium or electrolytes
Anemia	Pallor, poor weight gain, history of increased blood letting	Hb
Polycythemia	Plethora, dullness, jitteriness, feed intolerance	Hb

Management

Prevention

- Nurse the infant in servo-controlled radiant warmer or incubator to avoid fluctuations in body temperature
- Maintain head and neck in neutral/slightly extended position (use appropriate shoulder roll, if required).
- Maintain the patency of upper airway by gently removing the secretions, if present. Avoid vigorous suction. For feeding, orogastric tube is preferred over nasogastric tube as the latter increases airway resistance.
- Maintain oxygen saturation in range of 90% to 95% by rational use of supplemental oxygen. Hyperoxia should be avoided. Saturation should be monitored by continuous pulse oximetry.

Management

General measures

- Maintain airway, breathing and circulation.
- Clear airway by suctioning if required.
- Maintain environmental temperature in the lower end of thermo-neutral zone and avoid large swings.
- Oral feeding can be continued if the apnea is occasional and not severe. Avoid oral feeds in case of repeated episodes requiring positive pressure ventilation. Decreasing the volume of bolus feeding may be considered by giving feeds in small volumes more frequently (e.g. every one hour instead of every two hours).
- Treatment of the underlying cause: sepsis, anemia, polycythemia, hypoglycemia, hypocalcemia, respiratory distress syndrome (RDS)
- Transfuse packed cells, if required (follow transfusion guidelines)

Specific measures

Methylxanthines

Methyxanthines (Mx) are the mainstay of pharmacotherapy of AoP. *Mx therapy is not indicated for prevention of AoP or for secondary causes of apnea.*

Mx increases minute ventilation, improves CO_2 sensitivity, decreases hypoxic depression of breathing and periodic breathing and, enhances diaphragmatic contractility. The major mechanism of action is through competitive antagonism of adenosine receptors. Adverse effects include tachycardia, jitteriness, irritability, feed intolerance, vomiting and hyperglycemia.

There are two drugs in Mx group for treating AoP-caffeine and aminophylline (theophylline). The efficacy of both the drugs is similar but caffeine has lesser side effects and better dosage convenience, as it requires once daily administration compared to thrice daily dosing of aminophylline.

Table 16.2: Comparison of caffeine citrate and theophylline

	Caffeine citrate[6]	Theophylline[7]
Half life (h)	25-371 hrs (Mean 101 hrs)	13-29 hrs
Dose	*Loading dose:* 20 mg/kg of caffeine citrate (10 mg/kg of caffeine alkaloid) *Maintenance dose*: 5-10 mg/kg/d of caffeine citrate (2.5 to 5 mg/kg of caffeine alkaloid)	*Loading dose*: 5-6 mg/kg *Maintenance dose*: 1.5-3 mg/kg Q8-12h
Therapeutic drug level	8-20 µg/mL	5-10 µg/mL
Toxicity	Broad therapeutic window	Narrow therapeutic window

What is evidence?

A recent Cochrane review regarding the use of Mx concluded that they are effective in reducing the number of apneic attacks and the need for mechanical ventilation 2 to 7 days after starting treatment.[8]

The 'caffeine therapy for apnea of prematurity (CAP)' trial[9] has shown that infants <30 weeks treated with caffeine have:

- Decreased Need for supplemental oxygen at a postmenstrual age of 36 weeks
- Shourter duration of respiratory support.

There is insufficient evidence to recommend the use of prophylactic caffeine in extremely preterm neonates. Cochrane evidence does not support the use of prophylactic Mx therapy for AoP.[10]

Management (Mx) therapy for AoP is indicated in following circumstances:

a) When apneic episodes are frequent, *or*

b) If the baby requires PPV for apnea that is unresponsive to tactile stimulation

Mx therapy is initiated as IV therapy. Oral formulation of both the drugs can be used in place of intravenous formulation once the infant is stable and tolerating oral feeds.[11]

Mx therapy should be continued until 34 weeks post-menstrual age and stopped thereafter if no episode of apnea has occurred in the last 7 days. Caffeine or aminophylline initiated in order to facilitate extubation may be stopped after 5 to 7 days of therapy.[12]

Mx therapy should be discontinued at least 5 to 7 days prior to discharge. This is especially relevant for caffeine because of its longer half-life.

Doxapram[13]

The evidence for efficacy and safety of doxapram therapy for treating AoP is limited. Moreover, doxapram is associated with serious side effects and hence it *should not be employed* in treating neonates with AoP.

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is usually administered using nasal prongs when clinically significant episodes persist despite optimal Mx therapy.[14] At CPAP level of 5 cm of H_2O, infants with AoP will have fewer episodes. This reduction is primarily related to significant reduction in episodes of obstructive and mixed apneas and the effect has been attributed to splinting open of the upper airways by the positive airway pressure.

Nasal intermittent positive pressure ventilation

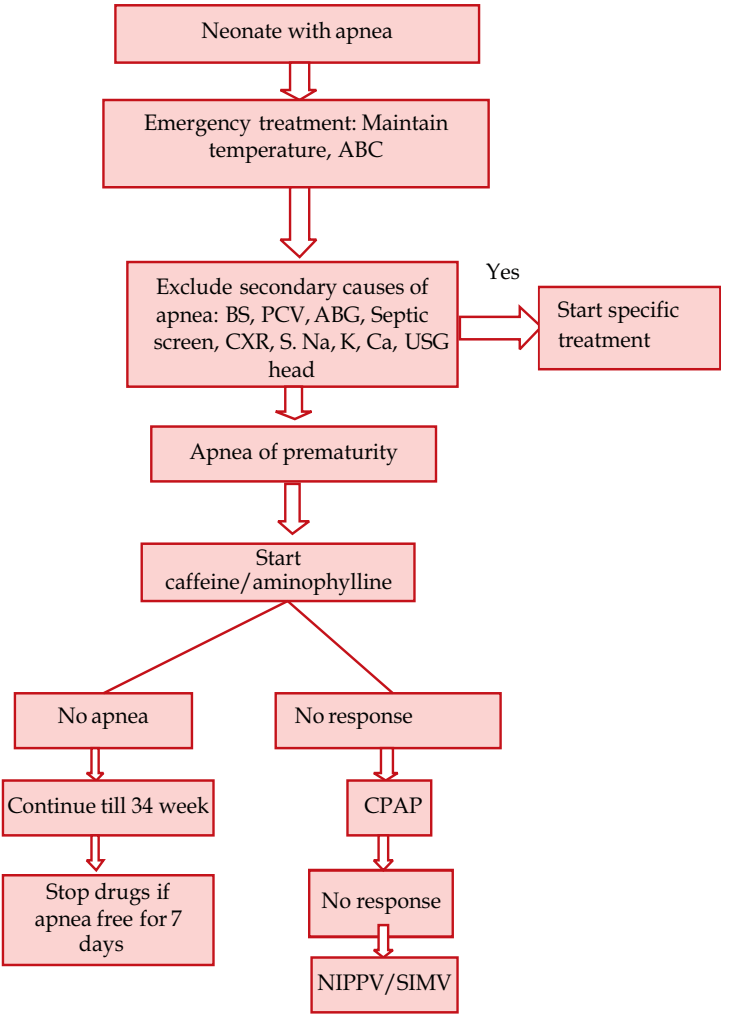
Infants with AoP and not responsive to Mx and CPAP therapy can be given a trial of nasal intermittent positive pressure ventilation (NIPPV). NIPPV may improve patency of the upper airway by creating intermittently elevated pharyngeal pressure. This intermittent inflation of the pharynx may activate respiratory drive by Head's paradoxical reflex, where in lung inflation provokes an augmented inspiratory reflex.[15] This results in resumption of breathing in neonates with apnea.

What is evidence?

A Cochrane review has shown the beneficial effect of nIPPV for treating preterm infants with apnea that are frequent or severe. It showed a greater reduction in frequency of apneas (events/hr) compared to nCPAP [WMD -1.19 (-2.31,-0.07)].[15]

Mechanical ventilation

The neonate should be ventilated if significant apnea persists despite both pharmacotherapy and CPAP. As there is no underlying lung disease in AoP, only minimal settings (PIP of



(ABC: airway, breathing, circulation; BS: blood sugar; PCV: packed cell volume; ABG: arterial blood gas; Na: sodium; K: potassium; Ca: calcium; USG: ultrasound; CPAP: continuous positive airway pressure; SIMV: Synchronized intermittent mandatory ventilation; NIPPV: Nasal intermittent positive pressure ventilation)

10-12 cm of H_2O and PEEP of 3-5 cm of H_2O, low rate of 20-25 per minute, short Ti of 0.35-0.40 seconds, and low FiO2 of 0.21 to 0.3) are required.

Persistent apnea

Apneic episodes may persist beyond 37 to 40 weeks in some infants, especially those born before 28 weeks of gestation. Mx therapy should be continued in such infants if apneic episodes continue to occur beyond 34 weeks of post-menstrual age. The neonate should be re-evaluated for secondary causes of apnea, especially neurological problems and gastro-esophageal reflux.

Sudden infant death syndrome (SIDS) and apnea

AoP is not found to be an independent risk factor for SIDS.

Neurodevelopment outcome[16-18]

The precise effect of fluctuations in breathing, heart rate and saturations during the episodes of apnea is not clearly defined. Retrospective studies have suggested that recurrent episodes of apnea are associated with worse neurodevelopment outcomes at 1-2 years of age. Prospective studies are required to define the association of apnea with neurodevelopment.

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