

## Apnea in the Newborn

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**Abstract**

Apnea, defined as cessation of breathing resulting in pathological changes in heart rate and oxygen saturation, is a common occurrence especially in preterm neonates. It occurs either due to immaturity of the central nervous system ( apnea of prematurity) or secondary to other causes such as metabolic disturbances etc . Secondary causes of apnea should be excluded before a diagnosis of apnea of prematurity is made. Methylxanthines and continuous positive airway pressure form the mainstay of treatment. Mechanical ventilation is reserved for apnea resistant to above therapy. An approach to the management of apnea in neonates has been described in this protocol.

## 1. Introduction

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

## 2. Definition

Apnea is defined as cessation of respiration for longer than 20 sec, or shorter duration in presence of cyanosis or bradycardia.<sup>1</sup>

## 3. Incidence

Apnea in preterm infants is usually related to immaturity of the central nervous system and is called apnea of prematurity (AOP). It can also occur secondary to other causes and is a common manifestation of most neonatal diseases. 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.<sup>1</sup>

## 4. Etiology of apnea<sup>2,3</sup>

**4.1. Apnea of prematurity(AOP) :** It is probably related to immaturity of the central nervous system. This condition usually presents after 1-2 days of life (the detection may be delayed by the presence of ventilatory support in the initial days of life) and within the first 7 days.

**4.2. Secondary causes:** Secondary causes of apnea include: (a) Temperature instability: hypothermia and hyperthermia, (b) Neurological: birth trauma, drugs, intracranial infections, intracranial hemorrhage, seizures, perinatal asphyxia, congenital myopathies

or neuropathies, placental transfer of narcotics, magnesium sulphate, or general anesthetics, central nervous system malformations, (c) Pulmonary: respiratory distress syndrome (RDS), pneumonia, pulmonary hemorrhage, obstructive airway lesion, pneumothorax, hypoxemia, hypercarbia, tracheal occlusion by neck flexion, (d) Cardiac: congenital cyanotic heart disease, hypo/hypertension, congestive heart failure, patent ductus arteriosus, increased vagal tone (e) Gastro-intestinal: gastro esophageal reflux, abdominal distension, (f) Hematological: anemia, (g) Infections: sepsis, pneumonia, meningitis, necrotizing enterocolitis, (h) Metabolic: acidosis, hypoglycemia, hypocalcemia, hyponatremia, hypernatremia and, (i) Inborn errors of metabolism.

**AOP is a diagnosis of exclusion and should be considered only after secondary causes of apnea have been excluded. Common causes of secondary apnea include sepsis, pneumonia, asphyxia, temperature instability and anemia.**

## **5. Types of apnea<sup>4</sup>**

**5.1 Central apnea:** (40%) Central apnea is characterized by total cessation of inspiratory efforts with no evidence of obstruction.

**5.2 Obstructive apnea:** (10%) In obstructed apnea, the infant tries to breathe against an obstructed upper airway, resulting in chest wall motion without airflow throughout the entire apneic episode

**5.3 Mixed apnea:** (50%) Mixed apnea consists of obstructed respiratory efforts usually following central pauses.

Purely obstructive apnea in the absence of a positional problem is probably uncommon.

## 6. Monitoring

All babies less than 34 weeks gestation should be monitored for at least in the first week of life or till absence of apneic episodes for at least 7 days. Babies  $\geq 34$  weeks gestation should be monitored if they are sick.

## 7. Apnea monitors<sup>5</sup>

**7.1 Pulse oximeters:** These are commonly used for monitoring of apnea. These monitors detect changes in heart rate and/ or saturation due to apneic episodes. Facility for detecting chest wall movement is absent in these monitors.

## 7.2 Other apnea monitors

### ***Movement sensors:***

- (i) Ripple type mattress
- (ii) Mattress with sensory pad
- (iii) Pressure sensitive capsule

These monitors interpret chest/ abdominal movements as respiration. In general, these monitors will fail to diagnose obstructive apnea and may not distinguish body movements from breathing.

***Thoracic impedance based monitors:*** These monitors translate changes in thoracic impedance that occur with breathing as respiratory activity. Like the movement sensors, these monitors also fail to diagnose obstructive apnea.

***Respiratory inductive plethysmography:*** It uses abdominal and thoracic movements during respiration. Abdominal thoracic bands or the Graseby capsule are used, the inductance of which changes with breathing.

**Magnatometer:** Electrical signal produced by chest or abdominal movement then can be detected by the sensor.

***Apnea monitors based on chest wall movement are likely to miss obstructive apnea.***

***Monitors with facilities for measuring heart rate and oxygen saturation would be more useful in the monitoring of significant apnea in preterm infants.***

## **8. Differential diagnosis**

**8.1 *Periodic breathing:*** It consists of breathing for 10-15 seconds, followed by apnea for 5-10 sec without change of heart rate or color.

**8.2 *Subtle seizures:*** Apnea is an uncommon presentation of a neonatal seizure in preterm infants. Sudden alteration in muscle tone, twitching movements, vacant stare and up rolling of eyes suggests a seizure. Also tachycardia preceding/ accompanying an apneic attack usually suggests seizure activity.

## **9. Evaluation of a child with apnea**

### **9.1 *Emergency treatment***

The neonate should be checked for bradycardia, cyanosis and airway obstruction. The neck should be positioned in slight extension; oro-pharynx gently suctioned, if required and tactile stimulation should be given. Most apneic spells respond to tactile stimulation. Oxygen by head box or nasal cannula is provided if the infant is hypoxic (maintain saturation between 90-93%). If the neonate continues to remain apneic and does not respond to tactile stimulation, ventilation with bag and mask (BMV) using 100% oxygen should be initiated. If BMV fails to initiate spontaneous respiration in the newborn, then the infant should be managed with positive pressure ventilation.

### **9.2 *Clinical examination***

After stabilization, the infant should be evaluated for a possible underlying cause. History should be reviewed for possible causes of secondary apnea including perinatal asphyxia, maternal drugs, neonatal sepsis and feed intolerance. The infant should be examined for temperature instability, hypotension, jaundice, pallor, cardiac murmur for PDA and poor perfusion. Onset of apnea within the first 7 days in a premature infant (gestation < 34 weeks) would be suggestive of apnea of prematurity (AOP).

### **9.3 Investigations**

Neonates with apnea should be investigated to exclude common causes of secondary apnea. Investigations that should be considered include blood glucose, hematocrit, electrolytes, septic screen, blood culture, arterial blood gas, chest x-ray, abdominal x-ray, ultrasound head and other investigations depending on the history and physical examination.

## **10. Treatment**

### **10.1 General measures:**

- Maintain airway, breathing and circulation
- Avoid vigorous suctioning of oro-pharynx
- Avoid oral feeds in case of repeated episodes of apnea requiring BMV.
- Decrease environmental temperature to lower end of thermo-neutral range. Avoid swings in environmental temperature.
- Treatment of the underlying cause: sepsis, anemia, polycythemia, hypoglycemia, hypocalcemia, respiratory distress syndrome (RDS).
- Transfuse packed cells if hematocrit <30%.

## **10.2 Specific measures for AOP**

Specific measures include:

- Drugs including aminophylline, caffeine, doxapram
- Continuous positive airway pressure (CPAP)
- Mechanical ventilation
- Kinesthetic stimulation

## **11. Pharmacotherapy for AOP**

Aminophylline, caffeine and doxapram have been used in the treatment of AOP. The indications for starting drugs are:

- For treatment for apnea of prematurity.<sup>6</sup>
- Post extubation to reduce the incidence of apnea.<sup>7</sup>

### **11.1 Methylxanthines**

***Methylxanthines have been the mainstay of pharmacologic treatment of AOP.*** Xanthine therapy increases minute ventilation, improves CO<sub>2</sub> sensitivity, decreases hypoxic depression of breathing, enhances diaphragmatic contractility, and decreases periodic breathing. The major mechanism of action is likely through competitive antagonism of adenosine receptors. Adenosine acts as an inhibitory neuro-regulator in the central nervous system and is released during hypoxia. Neonates exhibit hypoxic respiratory depression, and the ability of methylxanthines to block this response may contribute to their effect on *apnea*. A recent Cochrane review of the use of methylxanthines concluded that methylxanthines are effective in reducing the number of apneic attacks and the use of mechanical ventilation.

The loading dose of intravenous aminophylline is 5 to 6 mg/kg, followed by 1.5 to 3 mg/kg every 8 to 12 hours. Oral theophylline can be administered once the infant becomes stable in the same dose. Caffeine available for both oral and intravenous use has some advantages over theophylline. Because it has a higher therapeutic index, toxicity is less of a concern. Also, once-daily dosing is possible due to its longer half-life. A typical loading dose of 20 mg/kg caffeine citrate is followed in 24 hours by 5 to 8 mg/kg per dose, administered once every 24 hours. Recommended therapeutic levels are 5 to 10 µg/ml for aminophylline and 8 to 20 µg/ml for caffeine.<sup>8</sup> Aminophylline should be continued till 34 weeks corrected gestational age and stopped thereafter if no episodes of apnea have occurred in the last 7 days. Aminophylline initiated in order to facilitate extubation may be stopped after 7 days.<sup>9</sup>

Elimination of methylxanthines is prolonged in infants especially in preterm neonates. Xanthine therapy should be discontinued at least 1 to 2 weeks prior to

discharge, a guideline that is especially relevant for caffeine because of its longer half-life. Do not discharge the patient until methylxanthines have been stopped. There is no role for prophylactic use of methylxanthines for prevention of apnea, bradycardia, or desaturation in premature infants.<sup>10</sup> Adverse effects include tachycardia, jitteriness, irritability, feed intolerance, vomiting and hyperglycemia.

The drug is available as:

Injection: Aminophylline ampoule 250 mg per 10-ml ampoule.

Oral: Theophylline 50 mg/5 ml in Theoped syrup

***Caffeine: The drug is not available in India at present.***

### **11.2 Doxapram<sup>11,12</sup>**

Intravenous Doxapram might reduce AOP in the short term. The possible effects of treatment are usually not sustained after 48 hours of commencement of doxapram treatment. More over, doxapram is associated with serious side effects and hence should be used with caution or preferably avoided.

At present, indications for doxapram include failure to respond to both methylxanthine and CPAP therapy. The loading dose is preferably avoided. Doxapram infusion is started at 0.5 mg/kg/hour and increased gradually to a maximum of 2-2.5 mg/kg/hr. Doxapram may be tried for a period of 48 hours before weaning the drug. Methylxanthine therapy should be continued during doxapram infusion. Adverse effects include seizures, hypertension, hyperactivity, hyperglycemia and abdominal distension. It should be avoided in the first week of the life or if the serum bilirubin is high, because an association with intraventricular hemorrhage and kernicterus has been reported.<sup>13</sup>. Injection doxapram has 0.9% benzyl alcohol as a preservative. The recommended dose of

2-2.5 mg/kg/hr would deliver 21.6-32.4 mg/kg/day of benzyl alcohol. Although this dose is below the toxic dose of alcohol (45 mg/kg/day), there have been case reports of “gaspings syndrome” with this lower dose in literature.

#### **11.4 Which drug to use?**

Present evidence shows that aminophylline, caffeine and doxapram are equally effective in the treatment of AOP. However their clinical use is dependent upon adverse effects. The drug of choice would be caffeine, which is not available in India. Hence we prefer to use aminophylline as the drug of choice in the management of AOP.

### **12. Continuous positive airway pressure**

Continuous positive airway pressure (CPAP), usually administered using nasal prongs (NCPAP), is also an effective treatment of AOP and is typically used when clinically significant episodes persist despite optimal methylxanthine therapy.<sup>15</sup> At CPAP level of 5 cm water, infants with AOP will have fewer episodes. This reduction is primarily related to significant reduction in episodes of obstructive and mixed apneas and has been attributed to splinting open of the upper airways by the positive airway pressure. If NCPAP in conjunction with a methylxanthine, is not sufficient to prevent recurring episodes associated with bradycardia and intermittent hypoxemia, some investigators have suggested use of nasal intermittent positive pressure ventilation (NIPPV). NIPPV may most likely be needed when episodes are related predominantly to central apneas and are not effectively eliminated by the NCPAP.<sup>3</sup> CPAP may also be used to reduce post-extubation apnea in preterm infants.<sup>16</sup>

A CPAP of 5cm H<sub>2</sub>O is usually used. CPAP may be delivered by nasal prongs or nasopharyngeal tube. Endotracheal CPAP is not used in the treatment of apneic

spells. CPAP has no role in prophylaxis against apnea of prematurity. Adverse effects of CPAP include barotrauma, abdominal distension, feeding intolerance and local nasal irritation

### **13. Mechanical Ventilation**

The infant should be ventilated if both pharmacotherapy and CPAP have been tried and significant apneas continue to occur. If the lungs are normal, the infant should be ventilated at minimum pressures (peak inspiratory pressure of 10-12 cm of water and positive end expiratory pressure of 3-5 cm of water), low rate (20-25 per minute), short  $T_i$  (0.35-0.40 seconds) and low  $F_iO_2$  (0.3-0.5). This method is effective in all forms of apnea.

### **14. Kinesthetic stimulation**

Water bed, oscillating bed mattress. Present evidence does not support any role for this mode of therapy either in the prevention or treatment of apnea.<sup>17</sup>

### **15. Persistent apnea**

Apneic episodes may persist beyond 37-40 weeks in some infants, especially those born before 28 weeks of gestation. Methylxanthine therapy should be continued if apneic episodes continue to occur beyond 34 weeks of corrected gestational age. The neonate should be re-evaluated for secondary causes of apnea especially neurological problems and gastro-esophageal reflux. Home monitoring is not possible in our country and these infants would require NICU care until drugs can be weaned and stopped.

### **16. Sudden Infant Death Syndrome (SIDS) and Apnea**

AOP is not found to be an independent risk factor for SIDS. Only 2-4% of patients with SIDS have a history of AOP.

**17. Neurodevelopment outcome**

Most reports have found little evidence of any neurodevelopment risk directly attributed to a history of AOP. Precisely measured pre-discharge apnea related to AOP, however, has been reported to be predictive of lower developmental indices at two years.<sup>3</sup>

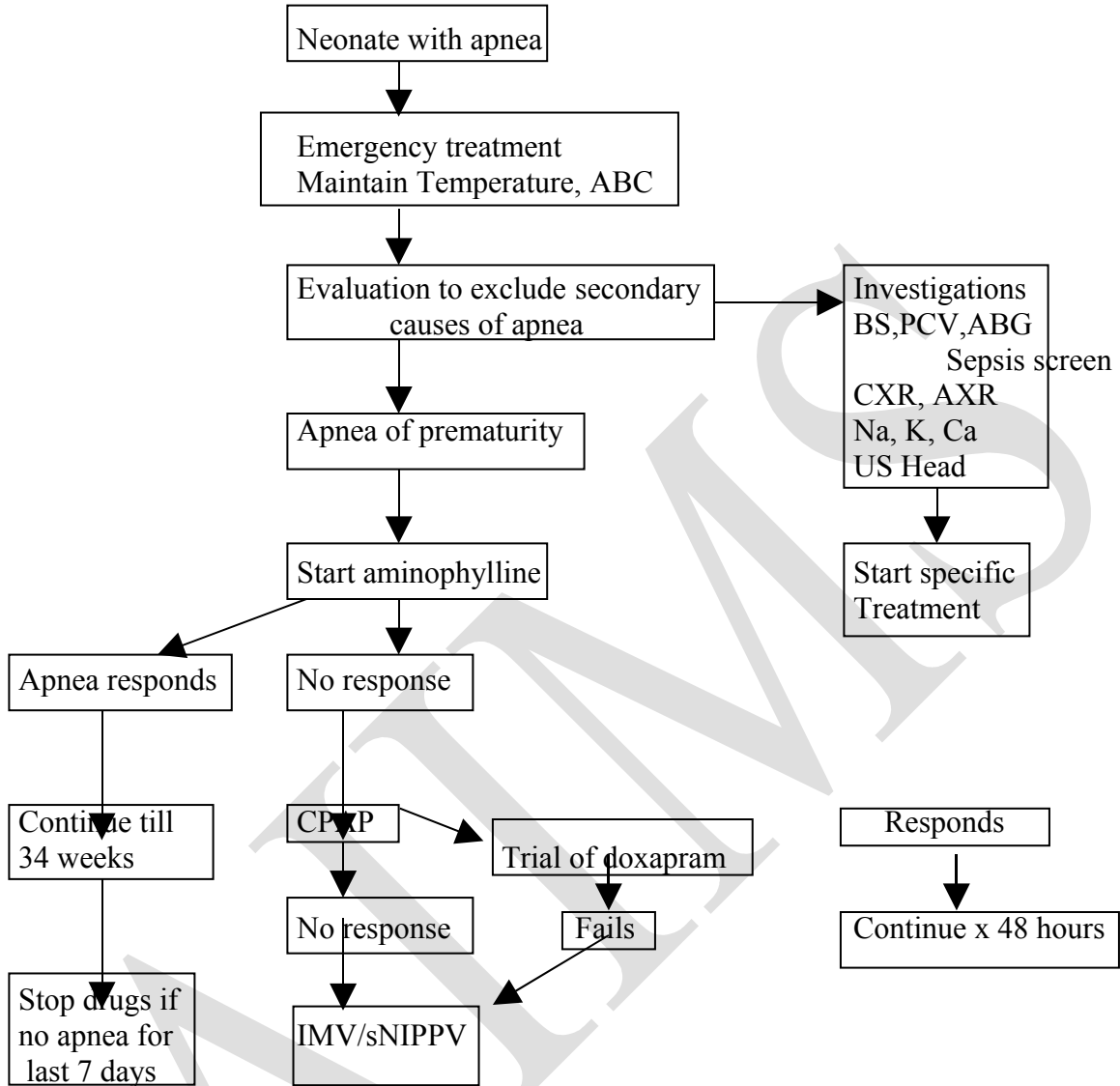
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**Algorithm for management of neonatal apnea**



(ABC: airway, breathing, circulation; BS: blood sugar; PCV: packed cell volume; ABG: arterial blood gas; Na: sodium; K: potassium; Ca: calcium; US: ultrasound CPAP: continuous positive airway pressure; IMV: intermittent mandatory ventilation ;sNIPPV : synchronized intermittent positive pressure ventilation )