Approach to apneic neonate

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INTRODUCTION:

- Apnea is defined as cessation of breathing or air flow for more than 20 seconds or shorter pause that is accompanied by bradycardia (heart rate <100beats per minute), cyanosis (oxygen saturation <80-85%) or pallor. (1)
- Apnea is more common in premature infants. Incidence of apnea is inversely proportional to the gestational age. Essentially, all infants born at less than 28 weeks of gestation diagnosed with apnea, beyond 28 weeks' of gestation incidence of apnea decreased from 85% in infants born at 30 weeks' gestation to 20% in those born at 34 weeks of gestation. Apneic spells usually stopped by 37 weeks of post menstrual age in infants born at 28 weeks of gestation. Apneic spells persistbeyond term gestation in infants born before 28 weeks of gestation. (2,3)
- Apneic spells occurring in term infants are always abnormal and are associated with identifiable conditions such as birth asphyxia, intracranial hemorrhage, seizures, structural abnormalities of central nervous system or depression from medications. (3)

CLASSIFICATION:

On the basis of presence or absence of respiratory effort and airflow apnea may be classified as:

Table no.1: classification of apnea

Types of Apnea	**Definitions**
Central apnea	Total cessation of inspiratory efforts with absence of airflow.
Obstructive apnea	Presence of respiratory efforts with absence of airflow.
Mixed apnea	Central apnea followed by obstructive apnea

- **Central apnea:** It is due to immaturity of central nervous system. In central apnea inspiratory efforts are absent but there no evidence of obstruction to airflow. Activation of laryngeal chemoreceptors can result in apnea, bradycardia and hypotension. Apnea due to laryngeal reflex can be induced by gavage feeding, aggressive suctioning, gastroesophageal reflux.
- **Obstructive apnea:** It caused due to obstruction to airflow usually at the level of pharynx. Mechanism leading to obstructed breaths includes instability of upper airway in preterm infants, lack of coordination of respiratory musculature. Neck flexion, anatomical abnormalities of upper airway and excessive secretions in the pharynx may cause obstructive apnea.

CAUSE AND DIFFERENTIAL DIAGNOSIS:

- Apnea in premature infants is due to immaturity of respiratory control system, immature response to hypoxia and hypercarbia and an abnormal response to stimulation of upper airways. There are many associated conditions that can aggravate the episodes of apnea. (4)

Table no.2: Differential diagnosis of apnea:

Infections	Meningitis, pneumonia, sepsis.
Temperature instability	Hypothermia, hyperthermia.
Central nervous system	Intracranial hemorrhage, seizures, birth asphyxia, CNS malformations.
Metabolic	Hypoglycemia, Hyponatremia, Hypocalcaemia,IEM.
Cardiac abnormalities	Patent ductus arteriosus, Congestive cardiac failure.
GIT	NEC, GERD.
Anatomical narrowing of airway	Choanal atresia, Micrognathia, Macroglosia, laryngomalacia.

Medications	Magnesium sulphate, general anesthesia, PGE1, Phenobarbitone, Midazolam, Fentanyl, Morphine.
Others	Prematurity, anemia, polycythemia

APPROACH TO DIAGNOSIS:

- All infants at risk of apnea (<35 weeks of gestation) should be monitored for at least first 7days after birth for apneic spells. Monitoring should be done by using pulse oximetry to detect episodes of desaturations and bradycardia. (3)
- After first episodes of apnea infant should be evaluated for specific underlying cause. Evaluation should include detailed history, physical examination of neonate, blood investigation and imaging.

Table no3: Evaluation of infants to exclude secondary causes of Apnea.

Associated clinical features	Possible Cause of apnea	Lab.and radiological Investigations
Lethargy, Refusal to suck, Poor perfusion, Feed intolerance, Abdominal distension, Hypo/Hyperthermia, Hypo/Hyperglycemia, Prolonged CRT, Metabolic acidosis.	Sepsis	CBC, CRP, blood culture, urine culture, CSF examination x-ray chest and abdomen
Jitteriness, Neuromuscular irritability, exaggerated startle and seizures.	Hypocalcemia	Measure ionic calcium level
Lethargic, difficulty in feeding, jitteriness, convulsions.	Hypoglycemia	Measure blood glucose level
Bounding pulses, wide pulse pressure, tachycardia, continuous murmur, hyperdynamic precordium, and mechanical ventilation requirement increased.	Patent ductus arteriosus (PDA)	Echocardiography X-ray chest.
Pallor, poor weight gain, Tachycardia, History of blood loss	Anemia	CBC
Plethoric, SGA, LGA, IDM, Hypoglycemia, Hyperbilirubinemia.	Polycythemia	Hb and PCV

Decreased reflexes, respiratory depression, CNS depression, Maternal history	Medications (MgSO4, anesthetics drugs, Anticonvulsants, sedatives)	History and measure specific drug level in blood.
Regurgitation of feed	GERD	Nuclear scan
Altered sensorium, seizures, Hypotonia, sudden onset of pallor , shock	Intracranial bleeding, birth asphyxia	Cranial USG.
Persistent vomiting, Peculiar odor, progressive encephalopathy, seizures of unknown cause, severe metabolic acidosis, persistent hypoglycemia.	Inborn error of metabolism	CBC, ABG , Electrolytes, Blood glucose, Ammonia, Lactate level, Urine ketones and reducing substances.

CAFFEINE:

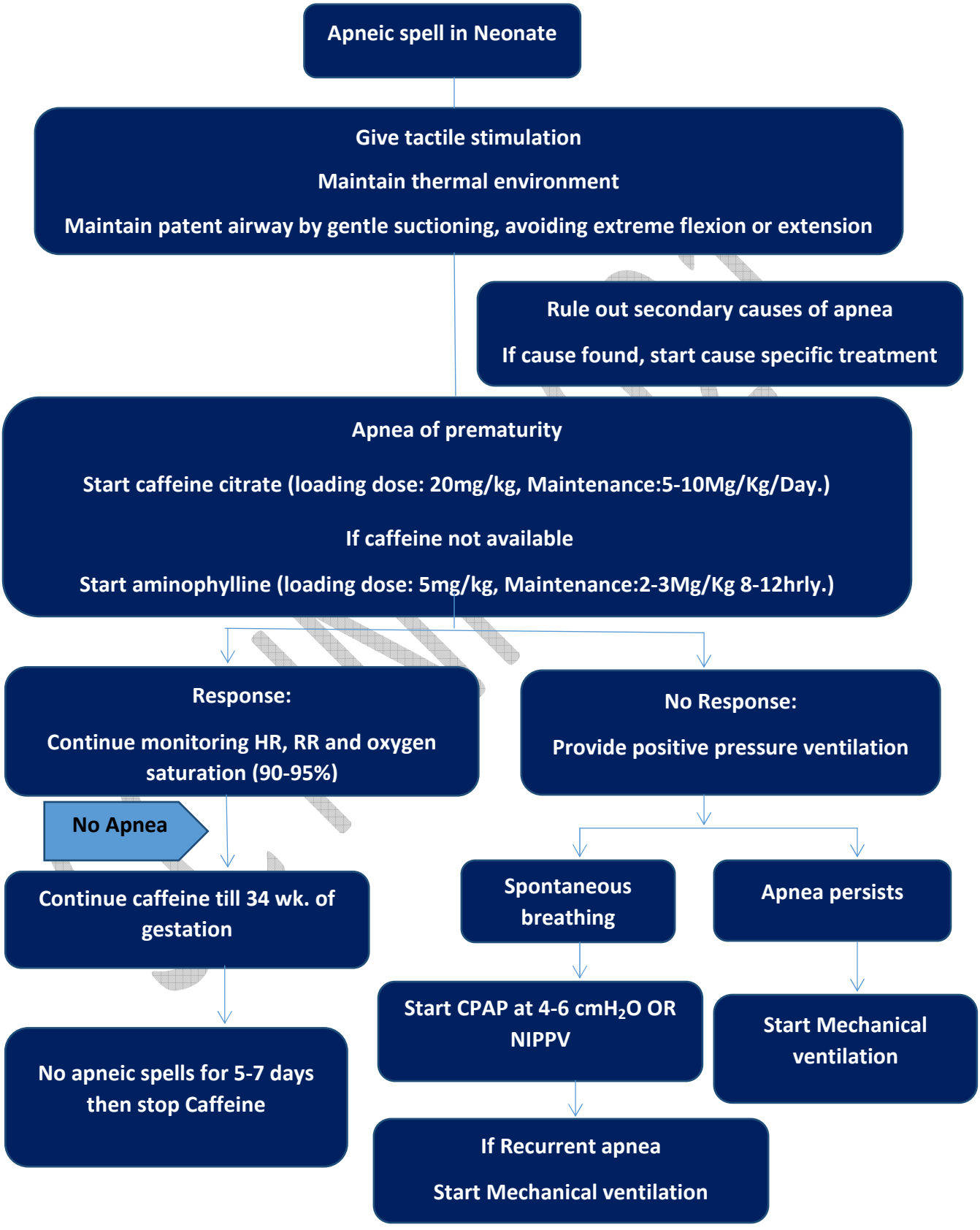
- Caffeine is the mainstay of pharmacologic treatment for apnea of prematurity. It reduces the frequency of apnea and the need for mechanical ventilation.
- Caffeine acts by inhibiting the adenosine receptors. Caffeine preferred over aminophylline because of its longer half-life (90-100h), high therapeutic index and lack of drug level monitoring.
- The effects of caffeine on respirations areincreased minute ventilation, improved carbon dioxide sensitivity, decreased periodic breathing, and decreased hypoxic depression of breathing.
- Caffeine therapy significantly improved the rate of survival without neurodevelopmental disability and reduced incidence of cerebral palsy and cognitive impairment, also reduced the frequency of BPD and incidence of severe ROP. Caffeine therapy for apnea of prematurity improved visuomotor, visuoperceptual, and visuospatial abilities at 11 years of age. (5,6)
- Prophylactic caffeine therapy: Prophylactic caffeine therapy in preterm infants less than 32 weeks decreased the duration of oxygen therapy, invasive and noninvasive ventilation, incidences of mild to moderate BPD, and length of hospital stay in preterm infants. (7)
- Caffeine may be administered by either oral or intravenous route.
- Standard Dose: loading dose 20 mg/kg followed by maintenance dose 5mg/kg. if apnea still persisted daily maintenance dose increase upto 10mg/kg.

- High dose caffeine therapy: loading dose 40 mg/kg/day and maintenance dose of 20 mg/kg/day may decrease the chances of extubation failure in mechanically ventilated preterm infants, duration of ventilation and frequency of apnea without any side effects. (8,9)
- Adverse effects: Tachycardia, feed intolerance, poor weight gain, jitteriness, sleep disturbance, seizures.
- Brands available: Capnea, Apnicaf, Cafirate, Primicaf, Caff-AOP, CAFWELL20, etc.

SUMMARY:

- Apnea is inversely proportional to gestational age of infant.
- Apnea of prematurity is a diagnosis of exclusion and should be considered after secondary causes ruled out.
- Preventive measures: Avoid extreme flexion and extension of neck, provide thermal environment, avoid aggressive nasal suctioning, maintain oxygen saturation between 90-95%.
- Caffeine reduces the number of apneic spells and the need for mechanical ventilation. If no apneic spells for 5-7 days, then stop caffeine therapy.
- If apnea persists despite of both caffeine therapy and CPAP/NIPPV then neonate should be mechanical ventilated.

Flowchart no.1: Management of apnea in neonate.



References:

1. Eichenwald EC and AAP COMITEE ON FETUS AND NEWBORN. Apnea of prematurity. Paediatrics.2016;137(1): e20153757.
2. Henderson-smart DJ. The effect of gestational age on the incidence and duration of recurrent apnea in newborn babies. AUST Paediatr J.1981;17(4)273-276.
3. Ann R. Stark. Apnea. In: Cloherty and starks Manual of neonatal care. Eric C. Eichenwald, Anne R. Hansen, Camilia R. Martin, Ann R. Stark, Naveen Jain(editors). South Asian Edition, Wolters Kluwer 2021. Pg.437-443.
4. Sale SM. Neonatal apnea. Best Pract Res Clin Anaesthesiol. 2010 Sep;24(3):323-36. doi: 10.1016/j.bpa.2010.04.002. PMID: 21033010.
5. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med. 2007;357(19):1893–1902.
6. Mürner-Lavanchy IM, Doyle LW, Schmidt B, et al. Neurobehavioral Outcomes 11 Years After Neonatal Caffeine Therapy for Apnea of Prematurity. Pediatrics. 2018;141(5): e2017404
7. Elmowafi M, Mohsen N, Nour I, Nasef N. Prophylactic versus therapeutic caffeine for apnea of prematurity: a randomized controlled trial. J Matern Fetal Neonatal Med. 2021 Mar 26:1-9. doi: 10.1080/14767058.2021.1904873. Epub ahead of print. PMID: 33771081.
8. Mohammed S, Nour I, Shabaan AE, et al. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. Eur J Pediatr. 2015 Jul;174(7):949-56. doi: 10.1007/s00431-015-2494-8. Epub 2015 Feb 3. PMID: 25644724.
9. Steer P, Flenady V, Shearman A, et al. Caffeine Collaborative Study Group Steering Group. High dose caffeine citrate for extubation of preterm infants: a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed. 2004 Nov;89(6): F499-503. doi: 10.1136/adc.2002.023432. PMID: 15499141; PMCID: PMC1721801.