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REVIEW

Apnea of prematurity: from cause to treatment

Jing Zhao · Fernando Gonzalez · Dezhi Mu

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Abstract Apnea of prematurity (AOP) is a common problem affecting premature infants, likely secondary to a "physiologic" immaturity of respiratory control that may be exacerbated by neonatal disease. These include altered ventilatory responses to hypoxia, hypercapnia, and altered sleep states, while the roles of gastroesophageal reflux and anemia remain controversial. Standard clinical management of the obstructive subtype of AOP includes prone positioning and continuous positive or nasal intermittent positive pressure ventilation to prevent pharyngeal collapse and alveolar atelectasis, while methylxanthine therapy is a mainstay of treatment of central apnea by stimulating the central nervous system and respiratory muscle function. Other therapies, including kangaroo care, red blood cell transfusions, and CO_2 inhalation, require further study. The physiology and pathophysiology behind AOP are discussed, including the laryngeal chemoreflex and sensitivity to inhibitory neurotransmitters, as are the mechanisms by which different therapies may work and the potential long-term neurodevelopmental consequences of AOP and its treatment.

Keywords Apnea of prematurity · Premature infant · Neurodevelopment · Methylxanthine therapy · Continuous positive airway pressure

J. Zhao · D. Mu (✉)
Department of Pediatrics, West China Second University Hospital,
Sichuan University,
Chengdu, China
e-mail: dezhi.mu@ucsf.edu

F. Gonzalez · D. Mu
Departments of Neurology and Pediatrics,
Newborn Brain Research Institute, University of California,
San Francisco, CA, USA

Introduction

During the first few days of life, premature infants encounter problems with temperature regulation, acquisition of oral feeding skills, and the normal control of respiration [85]. Resolution of apnea and establishment of a normal respiratory pattern is a major developmental milestone for many premature infants. The most widely used definition of apnea of prematurity (AOP) specifies a pause of breathing for more than 15–20 s, or accompanied by oxygen desaturation ($SpO_2 \leq 80\%$ for ≥ 4 s) and bradycardia (heart rate $< 2/3$ of baseline for ≥ 4 s), in infants born less than 37 weeks of gestation [55].

While AOP is a developmental disorder, the reasons behind the propensity for apnea in immature infants are not entirely clear. Although the pathogenesis of AOP is poorly understood, the immature pulmonary reflexes and breathing responses to hypoxia and hypercapnia likely contribute to the occurrence or severity of AOP [24, 70]. It may also be exacerbated by a number of coexisting factors or disease states [6, 52].

Severe apnea that lasts longer than 20 s is usually associated with bradycardia or desaturation, which may lead to disturbances of cerebral hemodynamics and possibly affect neurodevelopmental outcome. However, it is difficult to prove a link between apnea and poor neurodevelopmental outcomes due to a number of comorbidities and confounding factors affecting neurological development in premature infants. Therefore, evaluating the consequences of AOP on long-term neurodevelopment remains a challenge.

AOP treatment options are fairly limited and include prone positioning, methylxanthine therapy, and nasal intermittent positive pressure ventilation (NIPPV) or continuous positive airway pressure (CPAP) [34, 54, 63, 71].

Other reported treatments such as sensory stimulation, CO_2 inhalation, and red blood cell transfusions are not widely used and require further examination [3, 8, 13]. Since the pathogenesis and long-term neurodevelopmental effects of AOP are poorly understood, and the optimal treatment for AOP is not clear, this review discusses recent findings regarding pathogenesis, mechanisms underlying treatment, and consequences of AOP in premature infants.

Incidence

The incidence of AOP is inversely correlated with gestational age and birth weight. Seven percent of neonates born at 34 to 35 weeks gestation, 15% at 32 to 33 weeks, 54% at 30 to 31 weeks [50], and nearly all infants born at <29 weeks gestation or <1,000 g exhibit AOP [73]. It is generally broken down into three subtypes: central, obstructive, or mixed [85]. Central apnea accounts for approximately 10% to 25% of all cases of apnea, with obstructive apnea accounting for 10% to 25% and mixed for 50% to 75%. In each individual infant, one of these subtypes tends to predominate [85].

The incidence of bradycardia is fairly similar across these different groups; however, bradycardia does appear to occur more frequently with longer duration of apnea. Bradycardia occurs in 10% of apneic events with duration of 10–14 s, 34% of apnea lasting 15–20 s, and 75% of apnea that lasts >20 s. Bradycardia usually occurs following oxygen desaturation that is associated with apnea, with a recent study demonstrating an earlier onset of oxygen desaturation than bradycardia (median interval 4.2 s) [68]. However, recovery from bradycardia often precedes the recovery in oxygen saturation after apnea [68]. Bradycardia may also follow apnea without desaturation, possibly mediated by vagal nerve stimulation and not necessarily by hypoxemia.

Pathogenesis

AOP is a developmental disorder that self-resolves. In most cases, AOP likely reflects a “physiological” rather than a “pathological” immature state of respiratory control.

Fetal to neonatal transition

The fetus moves from an oxygen-poor environment, with PaO_2 of 23–27 mmHg, to an oxygen-rich environment after birth that provides a fourfold increase in PaO_2 [51]. The postnatal rise in PaO_2 effectively silences peripheral chemoreceptors, resulting in delayed onset of spontaneous breathing, especially when neonates are exposed to 100% oxygen during postnatal resuscitation [94]. Therefore, neonates need to quickly adjust their ventilation to adapt to the postnatal environment. The immature respiratory pattern and chemoreceptor function in premature infants may delay this postnatal adjustment, given fewer synaptic connections and poor myelination of the immature brainstem [25].

Ventilatory response to hypoxia

The ventilatory response to hypoxia after birth in premature infants elicits an initial transient increase in respiratory rate and tidal volume that lasts for 1–2 min, followed by a late, sustained decline in spontaneous breathing that may last for several weeks [31, 59]. This late decline in spontaneous breathing is termed hypoxic ventilatory depression, which may be associated with the delayed postnatal respiratory adjustment that occurs in premature infants.

Peripheral chemoreceptor stimulation may also lead to apnea secondary to hypocapnia seen after hyperventilation [17]. The CO_2 level can decrease to a level near the apneic threshold (1–1.3 mmHg below baseline CO_2 level) [42]. The relative proximity of the apneic threshold of CO_2, together with peripheral chemoreceptor activation in response to hyperventilation, may lead to apnea.

Ventilatory response to hypercapnia

In response to hypercapnia, premature infants increase ventilation by prolonging the period of expiration, but not increasing breath frequency or overall tidal volume, leading to less minute ventilation than that seen in term infants. This poor hypercapnic ventilatory response is more pronounced in premature infants with apnea than without apnea [24]. Contradictory movements of respiratory muscles in response to hypercapnia may also play a role in AOP. In a study of piglets exposed to hypercapnia, researchers found that resultant diaphragm activation prior to upper airway muscles activity results in obstructed inspiratory efforts and prolonged apneic events [18].

Ventilatory responses to laryngeal chemoreflex

Activation of the laryngeal mucosa in premature infants can lead to apnea, bradycardia, and hypotension [70]. While this response is assumed to be a protective reflex, an exaggerated response may cause AOP. This reflex-induced apnea is termed the laryngeal chemoreflex and is mediated through superior laryngeal nerve afferents [41, 83, 87].

Neurotransmitters and apnea

Enhanced sensitivity to inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA), adenosine, seroto-

nin, and prostaglandin, is another feature of the premature infant's respiratory control system [50]. GABA is the major inhibitory neurotransmitter in the CNS. In piglets, GABAergic neurons were activated during hypercapnia [99]. Blocking of $GABA_A$ receptors prevented ventilatory depression and increased respiratory rate in response to hypercapnia [78].

Adenosine is a product of adenosine triphosphate and is formed as a consequence of metabolic and neural activity in the brain, especially during hypoxia. Recent reports have found an interaction between adenosine and GABA in the regulation of breathing [1, 98]. This association is further strengthened by the observations that adenosine receptors are expressed in GABA-containing neurons. The binding of adenosine to its receptor may be involved with the release of GABA and thus inhibit respiration leading to apnea [98].

Genetic variability and apnea

Recently, researchers found that the heritability of AOP was 87% among same-gender twins [12]. These findings raise the possibility that AOP has an important genetic basis. Tamim et al. [86] first reported a higher proportion of first-degree mating for infants with AOP compared with those without AOP. Genomic studies may provide further information on the pathogenesis that underlies AOP.

Effects of sleep state and movements on apnea

Breathing and behavioral states are closely interrelated [44]. Premature infants spend a large proportion of their time in rapid eye movement (REM) sleep, with a relatively smaller amount in wakefulness. During REM sleep, these infants have more paradoxical breathing with a less stable baseline of oxygen saturation [69]. Therefore, apnea occurs more frequently in REM sleep than in quiet sleep [44, 74]. Arousal from REM sleep appears to be a precursor to apnea associated with oxygen desaturation in premature infants since motor activities after arousal are typically associated with laryngeal closure [44]. Therefore, movements frequently precede or occur simultaneously with apnea, and arousal from sleep may cause the apnea rather than terminate it.

Factors involved in apnea

While immature respiratory control is the primary cause of apnea in the premature infant, many coexisting factors can potentiate or worsen apnea. Apnea is a common presenting sign of both local and systemic infection [39, 84]. Apnea can be triggered by a number of central nervous system diseases, including intracranial hemorrhage, hypoxic-ischemic encephalopathy, and seizures. Thermoregulation may also play a role in apnea. Exposure to cooler temperatures decreased the duration and frequency of AOP, while elevated body temperature increased the incidence of AOP, suggesting that apnea is related to metabolic state and environmental temperature [91].

Other factors that have been associated with apnea in premature infants include glucose or electrolyte imbalance [85], as well as the presence of a patent ductus arteriosus with a large shunt [58]. A number of medications, including narcotic analgesics and magnesium sulfate, can lead to apnea in infants [85]. Anemia is also associated with apnea because of lowered oxygen-carrying capacity of red blood cells that leads to hypoxia, resulting in respiratory depression [11].

Gastroesophageal reflux and AOP are both occurring commonly in premature infants. However, the relationship between them remains controversial. Slocum et al. [89] set up a reflux model with rapid infusions of graded volumes of air into the esophagus of newborns to study this association. They did not find an association with apnea. Esophageal pH monitoring is the conventional method to test for the presence of acid reflux from the stomach [27]. Since infants receive frequent milk-based feedings, which continually buffer stomach acid, measured pH may be neutral or even alkaline in some cases [20]. Therefore, esophageal pH may significantly underestimate the frequency of reflux episodes in premature infants and may not identify AOP events resulting from nonacid reflux [20]. Multichannel intraluminal impedance technology has been used recently to monitor electrical impedance in the esophagus, which may provide a more comprehensive measure of reflux. In conjunction with pH measurement, multichannel intraluminal impedance can increase the sensitivity of reflux detection and the identification of both acid and nonacid reflux [21]. Even with these improved detection methods, researchers have not found an association between gastroesophageal reflux and apnea [56, 65]. Therefore, the majority of apneic episodes do not appear to be related to gastroesophageal reflux, though in a specific subset of events, a causal relationship may exist [80]. As a result, there is no evidence to support the use of anti-reflux medications for the treatment of AOP [89]. On the other hand, apnea may periodically lead to increased reflux. Recently, researchers found that the lower esophageal sphincter pressure was decreased during apneic episodes [61].

Other factors—including neck flexion, nasal obstruction, and delayed gastric emptying—have also been linked to apnea. Neck flexion interferes with neuromuscular regulation of pharyngeal patency and can produce intermittent airway obstruction [95]. Nasal edema or the presence of a nasogastric feeding tube also increases nasal airway resistance. Delayed gastric emptying can also increase

apneic events since abdominal distension reduces lung volume and increase vagal afferent feedback [88].

Interventions for premature infants with apnea

Interventions for AOP include efforts to reduce work of breathing and/or increase respiratory drive. The latest in AOP treatment will be discussed below.

Effective interventions

Prone position

Prone positioning can improve thoracoabdominal synchrony and stabilize the chest wall without affecting breathing pattern or SpO_2 [60]. Several studies have demonstrated that prone position reduces AOP [10, 69]. Extension of the neck 15° from the prone position is referred to as the head elevated tilt position, which has been found to decrease episodes of oxygen desaturation by 48.5% [77]. A more comfortable three-stair-position that maintains the head and abdomen in a horizontal position was reported to improve apnea, bradycardia, and desaturation [7]. However, head elevated tilt position has not been shown to work in combination with pharmacologic therapy. Recently, two randomized controlled trials investigated the effect of three different postural interventions on the incidence of bradycardia and desaturation. The researchers found that the effect of head elevated tilt position and three-stair-position interventions following aminophylline treatment was similar to standard prone positioning and only decreased the rate of desaturation by 12% [7, 71]. Thus, in infants receiving other effective treatment, neither head elevated tilt position nor three-stair-position resulted in a further improvement in AOP. Since head elevated tilt position and three-stair-position are easy to provide, it should be considered as a first-line intervention in infants with AOP.

Continuous positive airway pressure and nasal intermittent positive pressure ventilation

CPAP at 4–6 cmH_2O has proven a safe and effective therapy for AOP over the past 35 years. CPAP delivers a continuous distending pressure via the infant's pharynx to the airways to prevent both pharyngeal collapse and alveolar atelectasis. Therefore, CPAP can enhance functional residual capacity and reduce the work of breathing, improving oxygenation and decreasing bradycardia [26, 63]. CPAP works effectively to reduce the incidence of obstruction, but it has no clear efficacy in central AOP [53].

An extension of CPAP is the administration of NIPPV. Systematic meta-analysis has shown it to be effective in preventing extubation failure and for the treatment of AOP [45]. A randomized crossover trial [63] found that variable-flow nasal continuous positive airway pressure (NCPAP) is more effective in treating AOP than a conventional ventilator using NIPPV mode. In a word, reduced work of breathing may be the key to improving AOP, which can be achieved via either synchronized NIPPV [54] or variable-flow NCPAP devices [63].

Methylxanthine therapy

Methylxanthine compounds such as caffeine, theophylline, and aminophylline have been administered to premature infants as respiratory stimulants to decrease AOP [50]. These drugs are powerful central nervous system stimulants and likely reduce apnea by multiple physiological and pharmacological mechanisms. They are non-selective antagonists of adenosine receptors that increase minute ventilation, CO_2 sensitivity, and neural respiratory drive while decreasing the hypoxic depression of breathing. Methylxanthines also improve diaphragmatic contraction and respiratory muscle function [4, 34, 57].

Systematic reviews of caffeine therapy in AOP have shown that both caffeine and theophylline are effective in reducing apnea within 2 to 7 days of starting treatment. Caffeine is safer and has a wider therapeutic range than theophylline [12], and the plasma half-life of caffeine is 100 h compared to 30 h for theophylline [57]. A recent multicenter clinical trial has resolved the longstanding uncertainty about the long-term safety and efficacy of methylxanthine therapy as treatment for AOP. It revealed that caffeine reduced the rate of bronchopulmonary dysplasia and neurodevelopmental disabilities [75, 76]. Although the potential mechanisms of neuroprotective effect are not completely known, the decrease of ventilator-induced lung injury due to the use of caffeine may partly explain the neuroprotective outcome.

At what dose should caffeine be given? Because caffeine is usually available as caffeine citrate, the active component comprises only 50% of the total dose. In a study of caffeine for AOP, a loading dose of 10 mg⁄kg caffeine (i.v. or orally) and a maintenance dose of 2.5 mg⁄kg once daily worked efficiently [76]. A randomized controlled trial [82] compared three loading doses of 30, 15, or 3 mg/kg of caffeine followed by half of the loading doses every 24 h. The two higher dose groups had less apnea than the lowest dose group. In another randomized controlled trial, Steer et al. [81] compared a very high loading dose of 40 mg/kg caffeine (followed by 20 mg/kg every 24 h) with a standard loading dose of 10 mg/kg (followed by 5 mg/kg every 24 h). The high-dose group showed significant reductions in extubation failure, duration of ventilation, and apnea after extubation compared with the low-dose group. Thus, a higher dose of caffeine appears to

be more effective in preventing AOP. However, very high dose of caffeine was reported to have adverse effects. Hoecker et al. [35] found that a high loading dose of 25 mg/kg of caffeine reduced blood flow velocity in the cerebral arteries of premature infants by about 20%, whereas a loading dose of 10 mg/kg caffeine resulted in reduction of cerebral blood flow velocity that recovered 4 h post-dose [92]. Therefore, caffeine at a loading dose of 10 mg⁄kg followed by 5 mg⁄kg⁄day maintenance may be an adequate starting point. Only when refractory AOP persists should a switch to a higher dose be considered [81]. For theophylline use, the recommended loading dose is 5–6 mg/kg, followed by maintenance doses of 2–6 mg/kg/day divided into two or three daily doses [92].

Methylxanthines do carry some risks of adverse events. Toxic levels may produce tachycardia, cardiac dysrhythmias, and feeding intolerance or, at very high doses, may precipitate seizures. Mild diuresis and delayed gastric emptying can also be seen in very low birth weight infants. Methylxanthines also increase energy expenditure, possibly leading to diminished growth in premature infants, suggesting an extra caloric requirement is necessary in infants treated with theophylline [2, 19, 79].

Other interventions with unclear efficacy

Kangaroo mother care

Maternal kangaroo care, also known as skin-to-skin care for premature infants, has achieved widespread acceptance for stable infants because of the calming effects on the baby's clinical status and vital signs [30]. However, the effect of this approach for the treatment of AOP remains controversial. A randomized controlled trial showed that infants receiving kangaroo care had fewer apneic and bradycardic events than those who did not receive kangaroo care [46]. In a different study, researchers found that apneic and bradycardic events were increased during kangaroo care [16]. Recently, Heimann et al. [33] found that the effect of kangaroo care on improvement of apnea was the same as that seen with prone positioning. The use of kangaroo care for treatment of AOP still requires further study.

Sensory stimulations

Several studies suggest that sensory stimulants, including tactile and olfactory stimulation, are useful in the treatment or prevention of AOP. Tactile stimulation is the most common intervention in response to AOP. This simple intervention most likely works by generating excitatory, nonspecific neuronal activity in the brainstem center to stimulate respiratory activity [32]. An older randomized controlled trial showed that tactile stimulation reduced the frequency of apnea by 35% [40]. However, cutaneous stimulation often arouses the infant and markedly affects breathing pattern in premature infants. Bloch-Salisbury et al. [13] have demonstrated that subthreshold stimulation for causing arousal from sleep to wakefulness could decrease apnea by approximately 65%. However, systematic review has shown that kinesthetic stimulation is not effective at preventing AOP [62].

Olfactory stimulation has also been used for the treatment of AOP. Pleasant odors elicited increased respiratory drive, whereas unpleasant odors caused decreased respiratory effort, during active sleep when apnea is more common [5]. Vanillin, a stimulus known to affect the olfactory nerve, was used to treat refractory apnea and bradycardia unresponsive to both caffeine and doxapram [49]. They found that patients exposed to 15 drops of vanillin had significantly fewer apneic episodes [49]. Therefore, researchers concluded that the presence of a pleasant odor helped the infants to better regulate their respiratory patterns. Since this experiment was performed for only 24 h, it is not known how long this beneficial effect persists.

CO_2 inhalation

CO_2 is the physiologic stimulus for breathing in mammals. Apnea occurs when the CO_2 baseline decreases below the apnea threshold. A rise in CO_2 of 1 to 2 mmHg above the apnea threshold will reduce or abolish apnea [38, 42]. Recently, a randomized controlled trial of theophylline versus CO_2 inhalation for treating AOP showed that inhalation of a low CO_2 concentration (0.8%) in premature infants is as effective as theophylline in decreasing apnea. This exposure to 0.8% CO_2 also had no effect on cerebral blood flow velocity [3]. The authors concluded that CO_2 may be a better treatment for AOP than methylxanthines. However, it is likely that infants will quickly accommodate to an inspiratory CO_2 concentration, and the effectiveness of long-term exposure is not known.

Orogastric feeding tube placement

An increase in upper airway resistance may also play a significant role in AOP. Nasogastric tubes have been documented to increase nasal airway resistance by 50% [15]. Therefore, orogastric feeding tubes are sometimes preferred in premature infants with apneic events. However, a recent randomized controlled trial showed that the placement of the feeding tube had no significant effect on bradycardia and desaturation [15]. There does not appear to be a benefit of using an oral instead of a nasogastric tube for feeding infants with AOP. Interestingly, transpyloric feedings, especially when limited to human milk, have recently been shown to be safe and reduce episodes of

apnea and bradycardia in premature infants with suspected gastroesophageal reflux in a retrospective single-center cohort study [47].

Thermoneutral range

A mild increase in body temperature in infants enhances the instability of the breathing pattern [72]. In a recent study, less apnea was found at an incubator temperature of 30.4°C than at 32.5°C [91]. Of course, a number of factors play a role in incubator and baby temperature, but overheating may be a factor in AOP. However, a specific environmental temperature to reduce the incidence or severity of AOP is not known, and more research is required.

Red blood cell transfusions

Anemia can lead to AOP, and a proposed mechanism to treat AOP is transfusion of red blood cells to increase oxygen carrying capacity. However, data on the effect of blood transfusion on AOP is not clear. Studies focusing on bradycardia caused by apnea showed no effect of transfusion in either mildly or severely anemic infants [96]. Recently, a randomized trial [8] comparing a liberal with restrictive transfusion pattern in premature infants found that infants had more frequent apnea in the restrictive transfusion group. Furthermore, a retrospective study on the risks and benefits of transfusions in extremely low birth weight infants found that transfusions were not associated with apnea frequency but were associated with increased risk of bronchopulmonary dysplasia and necrotizing enterocolitis [93]. Based on these conflicting data, we think that the evidence is insufficient to recommend transfusion to treat AOP in anemic infants.

Doxapram

Doxapram is a potent respiratory stimulant used for the management of apnea refractory to methylxanthine therapy [14]. The use of doxapram is controversial because of its reported adverse effects [14, 97]. The short-term side effects of Doxapram include irritability, elevated blood pressure, and gastric retention, which are usually seen clinically with doses above 1.5 mg/kg/h [9]. The long-term side effects of doxapram remain unknown. Dani et al. [23] evaluated the effects of doxapram on cerebral hemodynamics in premature infants, using cerebral Doppler ultrasonography and near-infrared spectroscopy. They found doxapram induced an increase in cerebral oxygen consumption and a decrease in oxygen delivery. This is probably mediated by a decrease of cerebral blood flow. Therefore, doxapram is not routinely recommended for AOP since its side effects and long-term benefits versus potential harm are concerning.

Consequences of AOP

Short-term consequences

In premature infants, desaturation and bradycardic episodes often occur along with apnea. Bradycardia usually begins after the onset of hypoxemia and can initially be accompanied by a rise in stroke volume [68]. However, prolonged apnea and bradycardia can decrease the systemic blood pressure and lead to cerebral hypoperfusion, which may contribute to hypoxic-ischemic injury of the immature brain [66].

Long-term consequences

The long-term consequences of apnea are controversial [64]. It is difficult to prove a link between apnea and poor neurodevelopmental outcomes due to the possible coexistence of neurological injury in premature infants.

In early studies, no differences in neurodevelopmental outcomes were found between AOP and control infants. Delayed mental and motor development was seen in both premature infant groups [43]. However, Janvier et al. [37] found that an increased number of AOP days were associated with neurodevelopmental impairment such as cerebral palsy and blindness at 3 years of age. Recently, researchers found that a higher frequency and severity of AOP were associated with a higher incidence of unfavorable outcomes or death [67]. One explanation for these findings is that multiple recurrent hypoxic and bradycardia following AOP may cause long-term cerebral dysfunction. However, these two studies did not establish whether apnea was a cause or a result of underlying cerebral dysfunction.

Whether persistent AOP may lead to sudden infant death syndrome was only recently clarified. The risk of sudden infant death syndrome in premature infants is three times higher than that of full-term infants [36]. However, the risk factors for sudden infant death syndrome in premature infants are strongly associated with maternal age, tobacco use, meteorological factors, and genetics but not AOP [22, 28, 48, 90].

Generally speaking, the lower the gestational age, the longer the period that AOP persists. AOP disappears in most infants by 36 to 40 weeks postconceptional age. However, extremely premature infants (24–28 gestational weeks) are at risk for experiencing apnea beyond 38 to 40 weeks postconceptional age [29].

Summary

Apnea is a very common symptom in premature infants. In the majority of infants, apnea is a time-limited problem, disappearing by term postconceptional age. The long-term

consequences of severe, recurrent apnea-associated bradycardia and desaturation are not known. Many interventions for apnea, including some pharmacologic therapies, physical or mechanical methods, remain unproven for long-term efficacy. Further investigation of the pathogenesis and consequences of apnea in premature infants will help us understand the long-term risks. In addition, more research is necessary to clarify optimal treatment regimens.

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