Noninvasive respiratory support in the NICU

CLINICAL EVIDENCE SUMMARY

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Introducing noninvasive respiratory support

THE PRETERM LUNG

Each year, approximately 15 million babies are born preterm with resulting complications. Preterm birth can have an impact on the baby's respiratory system as it interrupts the normal progression of lung development, which can impact lung function and physiology.[1]

There are three key phases that occur during normal lung development between 16 and 40 weeks gestational age (GA): the canalicular, saccular and alveolar phases. If any of these phases are interrupted, preterm neonates can be born with lungs that are stiff, underdeveloped and lacking in surfactant, which makes them more susceptible to respiratory conditions[1] (see Figure 1).

Many preterm babies are unable to maintain adequate respiratory function to support ventilation requirements and often require some form of respiratory support to assist efficient gas exchange. For many preterm neonates, noninvasive respiratory support can help to open the lungs, reduce the work of breathing and improve gas exchange.[2]

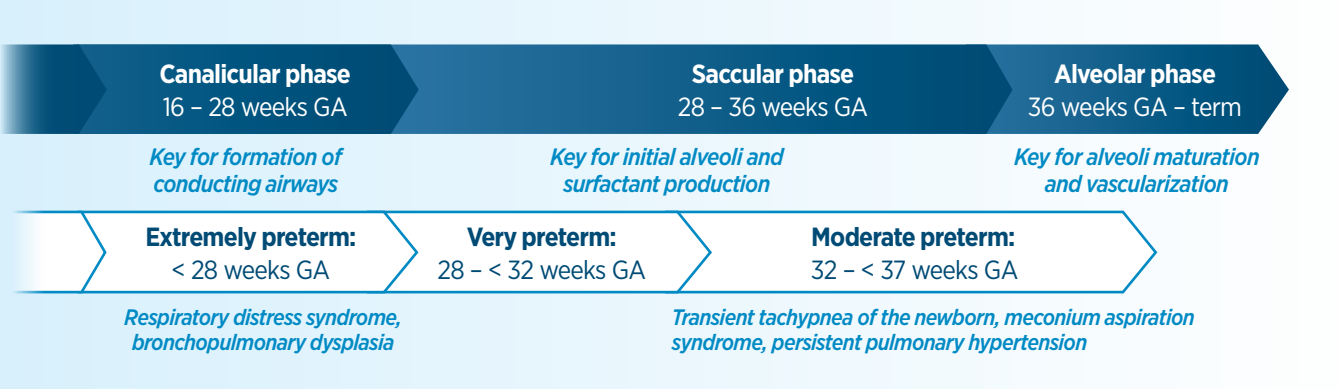


Figure 1. There are three key phases of lung development. When lung development is interrupted and babies are born preterm, they are more susceptible to different respiratory conditions.

INVASIVE MECHANICAL VENTILATION

Up to and including the 1970s, invasive mechanical ventilation was the primary strategy for preterm neonates unable to breathe spontaneously or maintain sufficient gas exchange. However, prolonged use can result in lung injury and inflammation, and is considered a primary risk factor for preterm neonates developing bronchopulmonary dysplasia (BPD).[3,4] In current practice, there has been a growing trend towards noninvasive respiratory support due to the risks associated with prolonged mechanical ventilation.[4] However, there are still some contexts in which invasive mechanical ventilation is required, as it provides an additional level of support to the most vulnerable neonates.[5]

NONINVASIVE RESPIRATORY SUPPORT IN PRETERM INFANTS

Noninvasive respiratory support refers to the delivery of respiratory support without the use of an artificial airway such as an endotracheal or tracheostomy tube. The umbrella term of noninvasive respiratory support covers a range of therapy options, which includes pressure-based therapies and flow-based therapies.

Pressure-based noninvasive therapies

Pressure-based therapy, also referred to as positive airway pressure therapy, continuously applies a distending pressure throughout the respiratory cycle. This generates a pressure gradient to allow heated, humidified gas to flow into the lungs while supporting the respiratory muscles to hold the lungs open between breaths.[3,6] The delivery of continuous distending pressure throughout the respiratory cycle is the key mechanism for distinguishing pressure-based therapies from flow-based therapies. Continuous positive airway pressure (CPAP) is one of the most widely used pressure-based therapies in neonatal intensive care units (NICUs). It has become an accepted alternative to invasive mechanical ventilation to treat neonatal respiratory distress syndrome and is considered the gold standard of care in providing noninvasive respiratory support. This is due to the range of benefits associated with pressure-based therapies, some of which include maintenance of functional residual capacity, reduction in the work of breathing, improved gas exchange and oxygenation.[7]

Interfaces designed to deliver CPAP

Interfaces are critical to the delivery of continuous distending pressure. They are designed to create and maintain a seal in the nares to ensure that the prescribed pressure can be delivered to the patient.[3,7,8] CPAP interfaces are specifically designed with larger tubes to lower the resistance to flow and help reduce the patient's work of breathing.[3]

The interfaces used to deliver CPAP include nasal masks, single nasal prongs, bi-nasal prongs, nasopharyngeal prongs (or long nasal prongs), nasal cannula and headbox enclosures. Of these, nasal masks and bi-nasal prongs are the most common interfaces used to deliver CPAP.[3]

Figure 2. Characteristics of a CPAP interface.

Flow-based noninvasive therapies

Nasal high flow (NHF) is a mode of noninvasive respiratory support that provides high flows of heated and humidified blended air and oxygen, through an unsealed interface to spontaneously breathing patients.[7,9] NHF is designed to deliver prescribed flow rates that meet or exceed the baby's peak inspiratory demand. When adequate flow rates are set, the mechanisms associated with NHF therapy, including the washout of anatomical dead space, delivery of dynamic positive airway pressure and improved warming and humidifying of respiratory gases, may be achieved[7,9] NHF is increasingly being used as an alternative form of respiratory support for preterm neonates with respiratory illnesses.[2]

Interface design to deliver NHF

NHF is designed to be an open system by using an unsealed interface. There are three characteristics which distinguish NHF interfaces from those used for pressure-based therapies. These interfaces are designed to deliver a prescribed flow rate and be unsealed in the nares. Additionally, they are designed with narrower tubes compared with CPAP, to increase the resistance to flow.

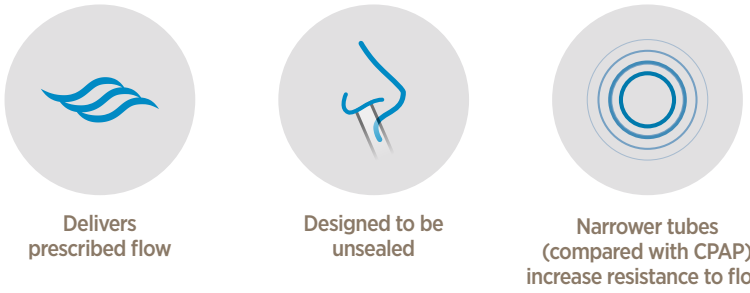


Figure 3. Characteristics of a NHF interface.

KEY POINTS

- To avoid complications associated with invasive mechanical ventilation, there is a growing trend towards noninvasive respiratory support for preterm neonates. CPAP and NHF are two therapies used as an alternative to mechanical ventilation.
- CPAP is a pressure-based therapy that delivers continuous distending pressure through an interface that is designed to be sealed.
- NHF is a flow-based noninvasive therapy that uses high flows of heated and humidified air and oxygen through an interface which is designed to be unsealed.

Understanding the mechanisms of action

There is an overlap in the key physiologic mechanisms delivered by pressure-based and flow-based therapies; however, the primary mechanism of each therapy is different. This is important to consider when choosing CPAP or NHF in preterm neonates.

HEAT AND HUMIDIFICATION OF RESPIRATORY GASES

Our airways naturally heat and humidify inspired air before it reaches the lungs, but in preterm neonates the ability to do this is impaired. Preterm neonates have an immature respiratory system with limited abilities for thermoregulation, impaired mucociliary transport and higher energy demands with low energy reserves. Therefore, the delivery of unheated and humidified gas (i.e., cold, dry gas) can adversely affect the airway mucosa and mucociliary function.[10]

The body of literature and clinical practice widely recommends the delivery of heated and humidified gas with noninvasive respiratory support. The delivery of heated and humidified gas minimizes the demand on the airways and maintains the mucociliary transport to improve mucociliary function, maintain airway mucosa and promote the conservation of energy for growth and development.[2]

CPAP: MECHANISMS OF ACTION

Maintains functional residual capacity

Functional residual capacity (FRC) is the volume of air that remains in the lungs after normal expiration and is important for keeping the lungs open between breaths.[2,11] For preterm neonates, especially those that have low compliance and surfactant deficient lungs, establishing an adequate FRC may be difficult. This encourages the small airways to close at expiration and increases the risk of alveolar collapse. This results in an increase in the respiratory effort required to establish and maintain FRC.

When CPAP is delivered, the continuous distending pressure provides an end-expiratory pressure which establishes and maintains FRC. This makes it easier for the patient to take the next breath as they don't have to exert additional energy to re-establish FRC. This results in improved lung volumes, which supports efficient gas exchange.[2]

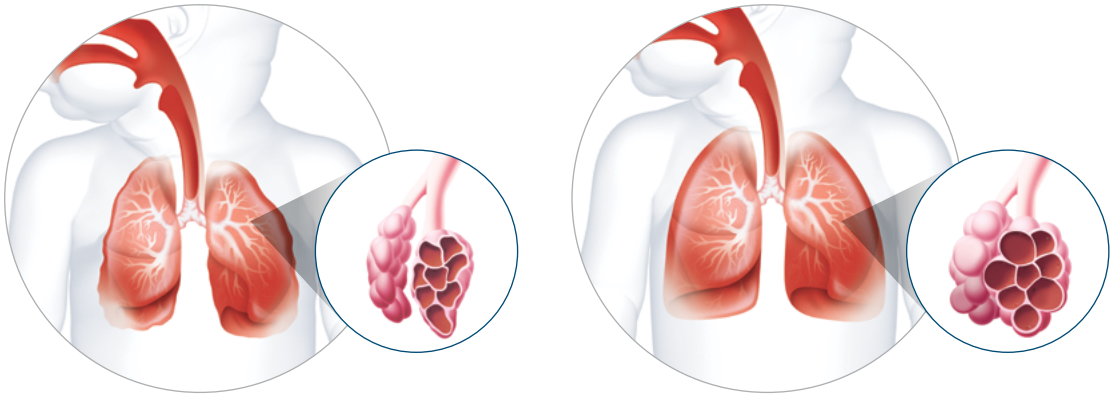


Figure 4. Image illustrating the effect of continuous distending pressure and CPAP therapy. In the absence of any positive airway pressure (left), FRC is decreased and resistance is high, resulting in alveolar collapse. With continuous distending pressure (right), FRC is maintained, reducing the risk of atelectasis.

Reduces work of breathing

The work of breathing (WOB) refers to the force required to expand the lungs against elastic and resistive forces, so that gas can move in and out of the lungs. CPAP provides a continuous distending pressure to elevate the end-expiratory lung volume and support the establishment and maintenance of FRC. This means that the patient doesn't have to work as hard to take the next breath, which works to promote patient comfort and efficient ventilation.[2,12]

Bubble CPAP generates pressure oscillations

The expiratory flow for bubble CPAP is vented to the atmosphere via a tube submerged in water. The set pressure can be controlled and adjusted by changing the depth of the tube within the water chamber. As the expiratory flow is generated, it creates a bubbling action which produces a back pressure to provide continuous distending pressure to the patient. When the bubbles burst, pressure oscillations are generated and transmitted down the airways. The combination of pressure oscillations and the continuous distending pressure are thought to provide a mechanism in which gas exchange may be improved and carbon dioxide (CO_2) eliminated.[13,14]

NHF MECHANISMS OF ACTION

Washout of anatomical dead space

Anatomical dead space refers to the upper airway volume where expired gas remains after each breath and does not undergo gas exchange.

In the absence of respiratory support, there is a high concentration of CO_2 in the upper airway (nasopharynx) at the end of exhalation. This CO_2 rich gas is then re-breathed on inspiration before fresh gas, and can increase the WOB for preterm neonates as they attempt to compensate for poor lung oxygenation to meet oxygen demand.[2]

Washout of the upper airways is considered one of the key mechanisms of NHF. If the set flow rate meets or exceeds the peak inspiratory demand, there is a continuous flow of fresh gas to wash out the CO_2-rich gas from the nasopharynx. During the next inspiration, CO_2 re-breathing is minimized and fresh gas is available for alveolar ventilation to support effective oxygenation, consequently reducing the WOB.[2,15]

Delivery of dynamic positive airway pressure

Most types of noninvasive respiratory support, such as CPAP, aim to promote an open airway by providing positive airway pressure throughout the respiratory cycle. NHF is an open system using an unsealed interface and is not intended to provide continuous distending pressure to the airways. However, when adequate flow rates are used, the continuous flow of gas enables resistance during expiration, which has been shown to contribute to a low level of positive airway pressure.[16]

The level of pressure that is generated during NHF is variable and hard to measure. It is also dependent on several factors, such as weight of the patient, set flow rate, and the level of nare occlusion and mouth leak.[17]

Many physiological studies have shown that NHF reduces the respiratory rate, inspiratory effort and the WOB when compared with no therapy (Figure 5).[18]

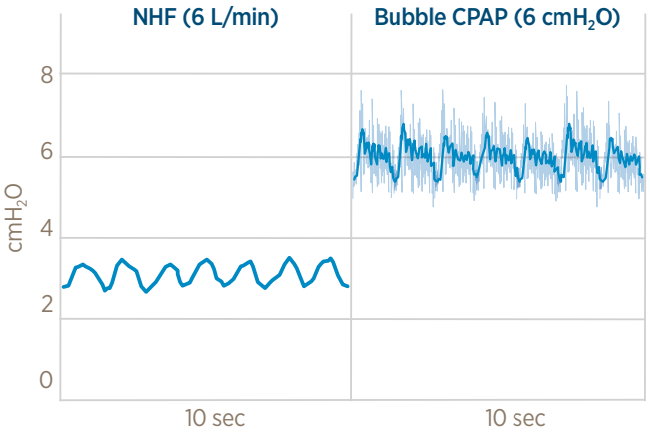


Figure 5. Graph showing the level of positive airway pressure generated with bubble CPAP and NHF.

KEY POINTS

Primary mechanisms of continuous positive airway pressure

- Heated, humidified gas
- Establishes functional residual capacity
- Reduces work of breathing
- Promotes gas exchange

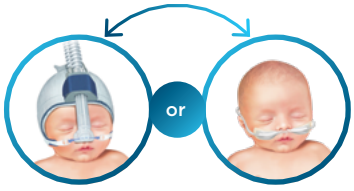
Primary mechanisms of nasal high flow

- Heated, humidified gas
- Washes out anatomical dead space
- Reduces work of breathing and improves oxygenation
- Improves patient comfort and tolerance to therapy (compared to CPAP)

Understanding when to use CPAP or NHF

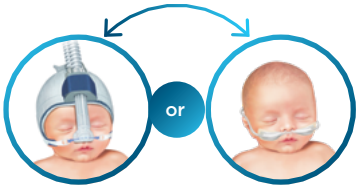
Clinical practice and the body of literature show that in preterm neonates <28 weeks GA, CPAP continues to be the gold standard of care for non-invasive respiratory support. This is likely due to compromised lung development and higher level of respiratory support required. However, there is increasing evidence supporting the use of NHF as an alternative to CPAP in preterm neonates >28 weeks GA that require a lower acuity of care or are more stable.
The clinical evidence has identified three different pathways in which CPAP and NHF can be used to support neonates >28 weeks GA:

Postextubation support



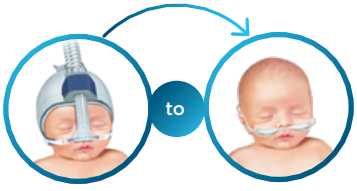
Wilkinson et al. 2016
Cochrane Review

Primary respiratory support



Bruet et al. 2021
Systematic Review

NHF as an alternative to prolonged CPAP



Roehr et al. 2016 and **Yoder et al. 2017**
Consensus

Figure 6. Clinical evidence suggests there are three different pathways in which CPAP and NHF may be used in neonates.

CPAP OR NHF AS POSTEXTUBATION SUPPORT

Wilkinson et al. 2016

There is extensive evidence to demonstrate the benefits of using CPAP or NHF as postextubation support. A Cochrane review (6 RCTs, 934 participants) compared the efficacy and safety of CPAP and NHF when used to support preterm neonates following extubation.[9] The population included preterm neonates ≥ 28 weeks GA with respiratory distress, randomized to receive either CPAP (2–8 cmH_2O) or NHF (flow rates 2–8 L/min).

There were no statistically significant differences between NHF and CPAP in the rate of therapy failure, reintubation, or adverse outcomes (i.e., pneumothorax). The results found that NHF was associated with a significant reduction in the rate of nasal trauma compared with CPAP. The authors concluded that NHF can be used as an alternative to CPAP for post-extubation support; however, it is recommended to have "rescue" CPAP available if therapy failure with NHF occurs.[9]

No statistically significant difference in **rate of treatment failure**	Typical relative risk: 1.21, 95% CI 0.95 to 1.55 Data from 5 studies, 786 neonates
No statistically significant difference in **rate of reintubation**	Typical relative risk: 0.91, 95% CI 0.68 to 1.20 Data from 6 studies, 934 neonates
No statistically significant difference in **adverse outcomes** i.e., pneumothorax.	Typical relative risk: 0.35, 95% CI 0.11 to 1.06 Data from 5 studies, 896 neonates
Significant reduction in **rates of nasal trauma with NHF**	Typical relative risk: 0.64, 95% CI 0.51 to 0.79 Typical risk difference: -0.14, 95% CI -0.20 to -0.08 Data from 4 studies, 645 neonates

CPAP OR NHF FOR PRIMARY RESPIRATORY SUPPORT

Bruet et al. 2021

Recent clinical evidence supports the use of NHF as primary respiratory support after stabilization, especially for neonates who require a lower acuity of care or are more stable. A systematic review by Bruet et al (2021) analyzed 10 randomized control trials to assess the efficacy and safety of NHF compared with CPAP when used as primary respiratory support.[19] The study population included 1,830 preterm infants < 37 weeks GA with respiratory distress randomized to receive CPAP (2–8 cmH_2O) or NHF (2–8 L/min).

The results showed that NHF was associated with a higher risk of initial therapy failure compared with CPAP; however, there were no significant differences in the rate of intubation due to the use of "rescue" CPAP when NHF therapy failure occurred. NHF was also associated with a lower risk of nasal trauma compared with CPAP.[19]

Higher risk of **therapy failure** compared with CPAP	(RR = 1.34, 95% CI 1.01 to 1.68, I^2 = 16.2%)
No significant difference in **intubation rates**	(RR = 0.90, 95% CI 0.66 to 1.15)
Lower risk of **nasal trauma with NHF**	(RR = 0.48, 95% CI 0.31 to 0.65)

The authors concluded that further research is required to understand which primary GA group NHF is suitable for within this application, but it may be a suitable alternative to CPAP in more mature preterm neonates.[19]

NHF AS AN ALTERNATIVE TO PROLONGED CPAP

Roehr et al. 2016, Yoder et al. 2017 and Clements et al. 2023

CPAP continues to be the gold standard in respiratory support for a large proportion of neonates with respiratory distress; however, recent studies and consensus guidelines have demonstrated that NHF may represent a suitable alternative to prolonged CPAP use.[20, 21] This can be used to either reduce the risk of adverse events such as nasal injury, air leak syndromes, or to wean from CPAP.[20, 21]

A randomized non-inferiority study assessed whether weaning from CPAP using NHF therapy was non-inferior to weaning using CPAP alone. The study population included 120 preterm neonates < 30 weeks GA with respiratory distress, who were randomized to 6 L/min NHF therapy, or bubble CPAP at 6 cmH_2O.[22] The results of this study found that weaning with NHF therapy was non-inferior to weaning with CPAP alone, with a shorter duration of respiratory support and lower rates of chronic lung disease for infants on NHF (18% vs. 36%). This study supports the use of NHF therapy as an alternative to prolonged CPAP when neonates are stable and ready to start weaning.[22]

KEY POINTS

- Clinical evidence shows that CPAP should be used in neonates < 28 weeks GA due to compromised lung development and the need for higher acuity of respiratory support. There is increasing evidence around the use of NHF in neonates >28 weeks GA who require a lower acuity of care or are more stable, while having "rescue" CPAP available should they fail NHF.

23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40

LESS THAN 28 WEEKS GA

CPAP first

for neonates with **compromised lung development** and a higher need for respiratory support.

FROM 28 WEEKS GA

NHF first with rescue CPAP

for neonates who **require a lower acuity of care or are more stable**. This approach may be considered as it provides two noninvasive options before needing to consider mechanical ventilation.

AIR LEAK SYNDROMES

Reference to a series of respiratory conditions that describe the leaking of air from the lung into extra-alveolar spaces. The resulting disorders depend upon the location of air. The most common air leak syndromes include pneumothorax, pulmonary interstitial emphysema, pneumatocele.

ALVEOLAR VENTILATION

The volume of gas that reaches the alveoli. This is measured either by a breath-by-breath basis or per minute.

BRONCHOPULMONARY DYSPLASIA (BPD)

A form of lung disease that develops in premature neonates treated with oxygen and positive-pressure ventilation, characterized primarily by arrest of alveolar and vascular development. Also defined as supplemental oxygen dependency for at least 28 days from birth and at 36 weeks corrected gestational age.
Also referred to as **Chronic Lung Disease (CLD)**.

CONTINUOUS DISTENDING PRESSURE

Continuous distending pressure applied to the lungs to expand them. Can be applied using continuous positive or negative airway pressure to create a partial vacuum.

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

Continuous positive airway pressure (CPAP) is a mode of noninvasive respiratory support that provides a continuous distending pressure throughout the respiratory cycle to spontaneously breathing patients.

Bubble CPAP
Continuous positive airway pressure therapy delivered via a bubble generator.

Ventilator CPAP
A valve within the ventilator creates the resistance to expiratory flow. Pressure is often varied by the size of the orifice.

Variable flow CPAP: Pressure is generated within the interface itself with help from the Venturi effect. Pressure is varied directly by flow rates.

DEAD SPACE

A volume of gas that does not participate in gas exchange. It is ventilated but not perfused by the pulmonary circulation. There are different types of dead space including: Alveolar, anatomic, mechanical, physiological.

Alveolar dead space
Volume of gas ventilating unperfused alveoli that has no blood perfusion (Shunt or pulmonary embolism).

Anatomic dead space
Volume of gas within the conducting zone of the lungs and upper airway (Amount of volume that does not fill enter the alveoli).

Mechanical dead space
Expired air that is re-breathed through connecting tubing.

Physiologic dead space
Anatomic and alveolar dead space.

ENDOTRACHEAL TUBE (ETT) OR TRACHEOSTOMY TUBE

Endotracheal tube
A tube inserted through the mouth or nose into the trachea to maintain an unobstructed airway. Most commonly used to ventilate lungs or administer therapeutic drugs.

Tracheostomy tube
A tube inserted through a tracheostomy to maintain an unobstructed airway. Most commonly used to deliver ventilation or administer therapeutic drugs.

FUNCTIONAL RESIDUAL CAPACITY (FRC)

The volume of air that remains in the lungs at the resting level or following a typical expiratory phase, important for keeping the lungs open post-exhalation and continuing passive gas exchange. The sum of expiratory reserve volume and residual volume.

GAS EXCHANGE

The diffusion of oxygen from the gas phase in the lung alveoli, through the alveolar-capillary membrane, into the pulmonary capillary blood, and of carbon dioxide in the opposite direction, both driven by partial pressure gradients.

LUNG COMPLIANCE

The ease with which the lung tissue can be expanded or stretched. Healthy lungs are stretchy and expand easily. A lung with low compliance is stiff and difficult to inflate. Lung compliance depends on the expansibility of both the lung tissue and thoracic cage and may be divided into static and dynamic compliance.

MUCOCILIARY TRANSPORT SYSTEM

Airway defense system which traps and neutralizes contaminants within mucus, before beating of cilia propagates it out of the airway.

NASAL HIGH FLOW (NHF)

A mode of non-invasive respiratory support that delivers high flows of heated and humidified, blended air and oxygen through an unsealed interface.

NASOPHARYNX

The part of the pharynx (throat) above the soft palate (the rear of the nasal cavity).

NEONATAL INTENSIVE CARE UNIT (NICU)

A hospital unit that provides intensive nursing and medical care for critically ill newborn infants.

PEAK INSPIRATORY DEMAND

Peak inspiratory demand is the maximum inspiratory flow rate required to achieve adequate ventilation.

PEAK INSIPIRATORY PRESSURE (PIP)

The highest pressure applied to the lungs during inspiration.

POSITIVE END EXPIRATORY PRESSURE (PEEP)

The positive airway pressure that is present after expiration is complete. PEEP is used in mechanical ventilation to improve oxygenation by stabilizing alveoli to remain open.

EXTUBATION

Withdrawal of an endotracheal tube (ETT) from a patient's airway.

PRETERM NEONATES

An infant born before 37 weeks gestation. They may be further divided by the degree of prematurity.

- Extremely preterm: < 28 weeks gestation
- Moderate to late preterm: 32 to < 37 weeks gestation
- Very preterm: 28 to < 32 weeks gestation

Note: Preterm neonates, preterm infants, and preterm babies may be used interchangeably.

RANDOMIZED CONTROLLED TRIAL (RCT)

Study design where participants are randomly allocated to receive or not receive clinical intervention(s) with the aim of comparing selected outcomes between these groups. Random allocation aims to reduce certain sources of bias.

RESPIRATORY DISTRESS SYNDROME (RDS)

A lung disease of the newborn, most frequently occurring in premature infants, where abnormally high alveolar surface tension as a result of lung surfactant deficiency impedes proper expansion of the lungs.
Also known as **Hyaline membrane disease (HMD)**.

RESPIRATORY RATE

The number of breaths taken over a specified period of time.

STATISTICAL SIGNIFICANCE

A statistical measure which helps to quantify whether a result is likely due to chance or a true relationship between variables. This can be represented by the p-value.

SURFACTANT

A substance produced in the lungs that reduces the surface tension of the air-liquid and helps to stabilize alveoli.

WORK OF BREATHING (WOB)

The force required to expand the lung against its elastic properties.

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