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# Mechanical Ventilation: Disease-Specific Strategies

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When noninvasive respiratory support is insufficient to achieve adequate gas exchange, insertion of an endotracheal tube and mechanical ventilator support may be necessary. Once it is determined that mechanical ventilation is needed, a variety of factors should be considered in choosing the mode of support. One factor is the type of mechanical ventilator to use: specifically either one of the "conventional approaches" or high-frequency ventilation. There are a number of conventional and high-frequency devices from which to choose; most are covered in greater detail in other chapters and will not be specifically addressed here. A second factor to be considered is the mode of ventilator support to be applied. Specifically, for conventional mechanical ventilation several different support modes may be selected on each device; again these are covered in more detail elsewhere in this book. A third factor to consider is the presumed benefits related to targeted gas exchange values and decreased work of breathing versus the relative risk of ventilator-induced lung injury (VILI). Perhaps most important, one needs to consider the underlying pathophysiology and its potential evolution over time. Finally, even from the time of initiating mechanical ventilator support, it is essential that the clinician has an active approach or plan for weaning and extubation (see also Chapter 24).

This chapter will discuss our approach to ventilator management in several of the most common neonatal respiratory disorders. It should be understood that there are a variety of devices and approaches other than those described here that one could employ resulting in safe, effective respiratory support of the ill neonate. Therefore, we will emphasize the key pathophysiologic features of each of the disorders and how the pathophysiology relates to the specific approach to mechanical ventilation. We firmly believe that the single most important factor associated with safe and successful ventilator management of the neonate is the person operating the device, not the device itself. A thorough understanding of the device, the mode applied, and the pathophysiology being managed, as well as a consistent, attentive approach to the specific infant being cared for, is essential to any success in managing respiratory problems in critically ill neonates.

## RESPIRATORY DISTRESS SYNDROME

It is indeed ironic that over 40 years after the introduction of continuous positive airway pressure (CPAP) as the first effective therapy for neonatal respiratory distress syndrome (RDS), and despite the marked technological advances that have been made during that time span, there has been a renewed emphasis on the application of noninvasive approaches, such as nasal CPAP, for respiratory support of neonatal lung disease.[1] Despite the increasing success with noninvasive respiratory support, many neonates still require mechanical ventilator support for RDS, particularly those at the lowest gestational ages, and these are the ones that will be addressed here.

### Key Pathophysiologic Features (Table 23-1)

#### Surfactant

A comprehensive overview of surfactant and its role in neonatal RDS is beyond the scope of this presentation. The reader is referred to Chapter 31 of this book and other publications for additional information.[2-5] Quantitative, qualitative, and metabolic disturbances in surfactant play key roles in the pathophysiology of neonatal RDS. The net effect is decreased compliance of distal airspaces that can lead to atelectasis, ventilation:perfusion mismatch, and intrapulmonary shunt.[2,5] Surfactant proteins play a critical role not only in the function of surfactant but also in the lung's response to infection. The indications for and approach to surfactant replacement therapy for neonatal RDS continue to be an area of very active investigation and will not be addressed in this chapter.[6-8]

#### Lung Liquid

Normal lung growth is regulated, in part, via fluid secreted into the potential airspace across the alveolar epithelial cells. Lung liquid secretion is generated via upregulated $Cl^-$ channels that actively transport $Cl^-$ into the lung lumen, with $Na^+$ and $H_2O$ following via an osmotic gradient.[9] During fetal life the epithelial $Na^+$ channel that promotes $Na^+$ and fluid absorption from the airspace in postnatal life is downregulated. Delayed upregulation of all three subunits of the epithelial $Na^+$ channel has been found in preterm infants with RDS, persisting in some to at least 1 month of age.[10] Additional factors that may contribute to persistent fetal lung liquid formation and delayed reabsorption of airspace fluid following preterm delivery include variable expression and activity of aquaporin channel proteins and persistent function of the secretory $Cl^-$ channels.[11]

#### Developmental Lung Biology

Development of the mammalian lung is a complex, highly orchestrated process that is subject to interruption from numerous insults, particularly premature birth. The progressive stages of lung development are well described and include embryonic, pseudoglandular, canalicular, saccular, and alveolar stages.[12] Vasculogenesis and angiogenesis, processes critical to lung growth and differentiation, are tightly connected throughout

**TABLE 23-1 Pathophysiology of Respiratory Distress Syndrome of Prematurity**

| Factor | Effect | Possible Intervention |
|---|---|---|
| Surfactant | Reduced quantity | Antenatal steroid therapy |
| | Impaired metabolism | Surfactant replacement |
| | Reduced surfactant proteins | Surfactant-specific proteins |
| | Disrupted function–proteins | Additional surfactant therapy |
| Lung liquid | Reduced clearance | Antenatal steroid therapy |
| | Sustained production | Postnatal steroid therapy |
| Mechanical | Reduced airspace compliance | Surfactant therapy |
| | High chest wall compliance | Positive end-expiratory pressure |
| | Increased airway compliance | Low inspiratory tidal volumes |
| Development | Canalicular–saccular stage | Antenatal steroid therapy |
| | Thickened mesenchyme | Maternal stress |
| | Immature capillary development | Effect of subclinical chorioamnionitis (?) |
| Inflammation | Altered surfactant metabolism | Antenatal steroid therapy |
| | Disrupted membrane integrity | Prevention/treatment of chorioamnionitis |
| | Interrupted lung development | Postnatal steroids and other antiinflammatories |

lung development. Postnatal viability first becomes possible for the human fetus during the latter phase of the canalicular stage, which occurs between 20 and 28 weeks' gestation, or approximately 50% to 70% gestation. During this stage, rudimentary air sacs begin to form off the terminal airways, simple interstitial capillaries begin to organize around these potential airspaces, and type I and type II epithelial cells begin to differentiate, with type II cells beginning to produce surfactant.[12] It must always be remembered that preterm birth, with subsequent exposure to increased ambient oxygen, unplanned gaseous inflation of the distal airspace, microbial colonization associated with prolonged tracheal intubation, and disturbances in nutrition, initiates a dramatic change in lung growth and development. The effects on lung growth and function, particularly at gestations of <30 weeks, may be lifelong, even for infants not diagnosed with bronchopulmonary dysplasia.[13,14] It is in the context of this immature stage of lung development, and the potential for adverse effects, that the following discussion on ventilatory support for neonatal RDS should be considered.

## Relevant Principles of Ventilation

In our neonatal intensive care unit (NICU) we most commonly use high-frequency oscillatory ventilation (HFOV) as the initial mode of support for those infants that require mechanical ventilation for neonatal RDS, at any gestational age. It is important to emphasize that there is no clear evidence that HFOV provides increased benefit (nor risk) compared to more conventional approaches to mechanical ventilation (i.e., volume targeted, surfactant treated) in terms of short-term outcomes such as initial gas exchange and subsequent diagnosis of bronchopulmonary dysplasia (BPD) prior to initial discharge.[15] Our approach to conventional ventilation, which is primarily volume targeted in nature, will also be discussed. Regardless

**TABLE 23-2 Indications for Trial of Noninvasive Respiratory Support**

| Indication | Comment |
|---|---|
| Consider noninvasive respiratory support initially for: | • All infants of ≥26 weeks gestation |
| After 10 minutes of resuscitation if: | • Indication for intubation has resolved but requires $FiO_2$ 0.3-0.5 to maintain targeted $SpO_2$ |
| After surfactant administration if: | • $FiO_2$ <0.4 and decreasing while maintaining targeted $SpO_2$<br>• No marked retractions<br>• No suspected airway obstruction<br>• >5 minutes since surfactant delivered |
| While on mechanical ventilation if: | • On high-frequency oscillation (see Table 23-4)<br>• On conventional ventilation (see Table 23-4) |
| Other | • Consider early/preextubation caffeine for infants of <32 weeks' gestation<br>• Wean/discontinue sedation/narcotics prior to extubation |

*$FiO_2$*, Fraction of inspired oxygen; *$SpO_2$*, oxygen saturation.

**TABLE 23-3 Possible Indications for Intubation and Mechanical Ventilation in Neonates**

| Indication | Comment |
|---|---|
| Infant of <26 weeks' gestation | Consider for prophylactic surfactant therapy (NB: recent evidence no longer supports this) |
| Absent/poor respiratory effort | Inadequate/sporadic effort, poor air entry |
| Apnea/bradycardia | Refractory; recurrent; requiring PPV |
| Hypoxemia | $FiO_2$ > 0.4-0.6 to maintain targeted $PaO_2/SpO_2$ |
| Hypercarbia | $PaCO_2$ > 60-65 mm Hg with pH < 7.20 |
| Severe distress | Marked retractions on noninvasive support |
| Suspected airway obstruction | Severe micrognathia, oropharyngeal mass, other |
| Cardiovascular collapse | Heart rate <60 or shock; CPR |
| Congenital malformations | Diaphragmatic hernia, choanal atresia, other |

*PPV*, Positive pressure ventilation; *$FiO_2$*, fraction of inspired oxygen; *$PaO_2$*, partial pressure arterial oxygen; *$SpO_2$*, oxygen saturation; *$PaCO_2$*, partial pressure arterial carbon dioxide; *CPR*, cardiopulmonary resuscitation.

of the mode of ventilation employed, the primary objective in the management of neonatal RDS is to minimize the initial use and/or duration of exposure to any form of invasive mechanical ventilation through aggressive application of early noninvasive modes of respiratory support (Tables 23-2 and 23-3), as well as the application of written guidelines to promote weaning and extubation from mechanical ventilation when applied (Table 23-4). The key to management includes recognition of the predominant pulmonary pathophysiology, which for RDS is typically a diffuse "alveolar" disease, coupled with the potential to disrupt immature lung development through pathways leading to or associated with VILI.[16-18] The management of the very preterm infant is additionally confounded by the underlying inflammatory milieu that is often present in association with clinical/subclinical chorioamnionitis and impaired intrauterine growth.[19-21] The key to all lung-protective ventilation strategies in infants with diffuse alveolar disease (i.e., diffuse microatelectasis) is the recruitment and maintenance of optimal lung

**TABLE 23-4 Guidelines for Recommending Extubation Based on Current Infant Weight, Mode of Ventilatory Support, and Ventilator Settings, Assuming Stable Airway and Minimal Apnea**

| | WEIGHT (G) | | | |
|---|---|---|---|---|
| | <1000 | 1000-2000 | 2000-3000 | >3000 |
| **High-Frequency Ventilation** | | | | |
| $\bar{P}_{aw}$ | 8 | 9-10 | 10-12 | 12 |
| $\Delta P$/amp | 16 | 18 | 20 | 22 |
| $FiO_2$ | <0.40 | | | |
| **PC-SIMV and PSV** | | | | |
| PIP | <16 | 16-20 | | 20 |
| PEEP | <6 | <7 | | <8 |
| PS | <6-8 | | | |
| $FiO_2$ | <0.40 | | | |
| Rate | 16-20 bpm | | | |
| **SIMV + VG and PSV** | | | | |
| PIP | <16 | 16-20 | | 20 |
| PEEP | <6 | <7 | | <8 |
| $V_T$ | 4-5 mL/kg | | | |
| PS | <6-8 | | | |
| $FiO_2$ | <0.40 | | | |
| Rate | 16-20 bpm | | | |

*$FiO_2$*, Fraction of inspired oxygen; *$\bar{P}_{aw}$*, mean airway pressure; *$\Delta P$/amp*, change in pressure (amplitude); *PIP*, peak inspiratory pressure; *PEEP*, positive end-expiratory pressure; *PS*, pressure support; *PC-SIMV*, pressure control–synchronized intermittent mandatory ventilation; *PSV*, pressure support ventilation; *$V_T$*, tidal volume; *VG*, volume guarantee.

inflation and avoidance of excessive tissue stretch. In our NICU, we are more comfortable achieving these goals with HFOV, although similar strategies can be achieved with conventional ventilation.

## High-Frequency Ventilation

With HFOV the key is to achieve initial airspace recruitment and then to maintain optimal lung inflation and gas exchange at the lowest acceptable mean airway pressure ($\bar{P}_{aw}$) (Tables 23-5 and 23-6). The process for achieving this goal includes (1) an initial stepwise escalation in $\bar{P}_{aw}$ to recruit atelectatic airspaces indicated by the ability to significantly reduce $FiO_2$ (commonly referred to as the "opening pressure" for the lung); (2) a subsequent stepwise reduction in $\bar{P}_{aw}$ to a point at which $FiO_2$ needs to be again escalated to maintain targeted $SpO_2$ (commonly referred to as the "closing pressure" for the lung); and (3) increasing the $\bar{P}_{aw}$ back above the closing pressure (typically by 2 to 3 cm $H_2O$ in surfactant-treated infants) to maintain an end-expiratory lung volume that allows effective gas exchange while minimizing pressure/volume effects on the cardiovascular system, thus "optimizing" oxygen delivery at the tissue/cellular level. A number of studies have described this approach using such measurements as $SpO_2$, respiratory inductance plethysmography, high-resolution computed tomography (CT) scan, and forced oscillatory technique.[22-25] Other than $SpO_2$, these tools are not currently available in most practice settings. We typically provide early surfactant replacement therapy to all preterm infants intubated for RDS and then begin the process of optimizing lung inflation. We do not usually reduce $\bar{P}_{aw}$ to closing pressure but more commonly will incrementally reduce the $\bar{P}_{aw}$ by 1 to 2 cm $H_2O$ once $FiO_2$ has been reduced to <0.25 (Table 23-7). Although radiographic lung volumes may not be ideal for assessing optimal lung inflation, when combined with clinical observations such as heart rate and blood pressure, as well as the temporal changes in $FiO_2$ and $SpO_2$, one can usually maintain adequate lung inflation and gas exchange while minimizing the risks of either overinflation or atelectasis.

Ventilation, or the removal of $CO_2$ during HFOV, is dependent on tidal volume ($V_T$) and rate. As described elsewhere in this book, $V_T$ has a relatively greater effect on minute ventilation than rate. Factors affecting $V_T$ during HFOV include lung compliance and resistance, inspiratory time, and the amplitude or power of the oscillatory breath. It is critical to remember that changes in frequency during HFOV can markedly affect $V_T$ (increased as frequency decreases and decreased as frequency increases). Dynamic changes in lung volume and compliance that accompany increased lung inflation can significantly affect not only oxygenation but also ventilation through effects on $V_T$.[24] As dramatic shifts can occur in $PCO_2$ during HFOV, we recommend either frequent blood gas assessment or transcutaneous $PCO_2$ monitoring during the initial implementation of HFOV, particularly in the most immature infants. As shown in Table 23-7, adjustments in amplitude are more commonly made in response to measured $PCO_2$ than are changes in frequency. We practice a mild permissive hypercarbia approach at all gestational and postnatal ages.[26-28] More pronounced hypercarbia has not been shown to be of benefit in a randomized trial.[29]

## Conventional Ventilation

Our approach to conventional ventilator support for neonatal RDS is almost always a volume-targeted, synchronized intermittent mandatory ventilation (SIMV) mode, unless a large (>50%) air leak occurs around the endotracheal tube, in which case we will use a pressure-controlled mode.[30] The same guiding principles should be used in initiating and adjusting support as noted above. Typical initial ventilator settings for SIMV are shown in Tables 23-5 and 23-6. We prefer to initiate support with slightly higher positive end-expiratory pressure (PEEP) values, in the 6- to -8 cm $H_2O$ range, in an effort to improve recruitment. Subsequent reductions in PEEP are based on $FiO_2$, $SpO_2$, and chest radiographs. $V_T$s are usually set at around 5 mL/kg; clinical assessment of chest movement as well as analysis of ventilator-derived lung mechanics is performed to ensure $V_T$ is adequate. If a pressure-controlled mode is required, usually due to excessive air leak around the endotracheal tube, we attempt to limit the peak pressure via clinical assessment as well as frequent monitoring of delivered $V_T$ (again targeting volumes of 4 to 6 mL/kg). We employ early caffeine therapy in infants of <32 weeks' gestation and attempt to minimize sedation to encourage spontaneous respiratory efforts. Pressure support is commonly employed to minimize work of breathing, yet encourage diaphragmatic activity, while intubated (Table 23-6).[31] The preference for SIMV is subjective, not evidence based; many other centers use assist/control or pressure support ventilation as the primary mode with equal success.

## Extubation

An aggressive approach to weaning and extubation is encouraged. This includes (1) written guidelines for weaning from

## TABLE 23-5 Suggested Initial Approach to Mechanical Ventilation by Condition and Ventilatory Mode

| Respiratory Disorder | Conventional Ventilation (Volume-Targeted, SIMV + PS, or A/C) | High-Frequency Ventilation |
|---|---|---|
| RDS | Surfactant therapy<br>Volume target ($V_T$) 4-6 mL/kg<br>Rate 30-60 bpm<br>I-time 0.30-0.35 seconds<br>PEEP 5-8 cm $H_2O$<br>PS to achieve ~¾ set $V_T$ | Surfactant therapy<br>Oscillator: Frequency 8-10 Hz; $\bar{P}_{aw}$ 10-16; $\Delta P$ ~2× $\bar{P}_{aw}$—adjust to vibrate chest/abd<br>Jet: Rate 360-420; PEEP as needed to optimize lung inflation (typically 7-10); minimal or no backup rate |
| MAS | Surfactant therapy; ±iNO<br>$V_T$ 5-6 mL/kg<br>Consider rate ≤30<br>I-time 0.35-0.50 seconds<br>PEEP 4-7 cm $H_2O$; set/adjust<br>Based on lung inflation<br>PS to achieve ~¾ set $V_T$ | Surfactant therapy; ±iNO<br>Oscillator: Frequency 6-8 Hz w/$\Delta P$ to vibrate chest/abd; $\bar{P}_{aw}$ as needed for ~9 rib lung inflations<br>Jet: Rate 240-360; may need increased I-time; minimal or no backup rate; PEEP as needed<br>Flow interrupter: Rate 240-360; convective rate 6-12; convective I-time ≥1 second; PEEP as needed |
| Lung hypoplasia/ diaphragmatic hernia | $V_T$ 4-5 mL/kg; PIP <26 cm $H_2O$<br>Rate 40-60 bpm<br>I-time 0.25-0.40 seconds<br>PEEP 4-6 cm $H_2O$<br>Surfactant only for RDS features | Oscillator: Frequency 8-10 Hz; $\bar{P}_{aw}$ @ 10-13 depending on weight; $\Delta P$ ~2× $\bar{P}_{aw}$—adjust to vibrate chest/abd; I:E 33%<br>Jet: Rate 360-420; PEEP 5-8 cm $H_2O$ as needed to optimize lung inflation; minimal/no backup rate |
| BPD, early/mild–moderate form<br>BPD, chronic–severe form | Volume-targeted: $V_T$ 5-8 mL/kg; rate 20-40 bpm<br>I-time 0.35-0.45 seconds<br>PEEP 5-8 cm $H_2O$<br>PS to achieve ~¾ set $V_T$<br>$V_T$: May need 6-10 mL/kg (or higher) owing to increased dead space<br>I-time 0.50-0.70 seconds; longer to overcome airway resistance<br>Rate 20-30 bpm; slower to allow adequate lung emptying<br>PEEP: Quite variable; may need 8-12 cm $H_2O$ to "stent" airway open | Oscillator: Similar to MAS<br>Jet: Similar to MAS except consider minimal backup rate to optimize lung recruitment<br>HFV not commonly applied for managing chronic–severe BPD; anecdotal reports suggest HFJV used with the "MAS approach" may be more effective than HFOV |
| PPHN | iNO as indicated<br>Avoid lung hyperinflation, correct atelectasis<br>Adjunct therapies | iNO as indicated<br>Optimize lung inflation, avoid both over- and underinflation<br>Adjunct therapies |

*ABD*, abdomen; *A/C*, Assist/control; *BPD*, bronchopulmonary dysplasia; *HFJV*, high-frequency jet ventilation; *HFOV*, high-frequency oscillatory ventilation; *HFV*, high-frequency ventilation; *I:E*, inspiratory to expiratory ratio; *iNO*, inhaled nitric oxide; *MAS*, meconium aspiration syndrome; $\bar{P}_{aw}$, mean airway pressure; *PEEP*, positive end-expiratory pressure; *PPHN*, persistent pulmonary hypertension of the newborn; *PS*, pressure support; *PIP*, peak inflation pressure; $\Delta P$, change in pressure (amplitude); *RDS*, respiratory distress syndrome; *SIMV*, synchronized intermittent mandatory ventilation; $V_T$, tidal volume.

## TABLE 23-6 Initial Recommended Settings for Mechanical Ventilator Support of Infants with Respiratory Distress Syndrome by Current Weight and Ventilatory Support Mode

| | WEIGHT (G) | | |
|---|---|---|---|
| **Mode** | **<1000** | **1000-2500** | **>2500** |
| **HFOV** | **Initial Settings** | | |
| Rate | 10 Hz | 10 Hz | 8-10 Hz |
| $\bar{P}_{aw}$ (cm $H_2O$) | 10-12 | 10-14 | 12-16 |
| $\Delta P$ | 2 × $\bar{P}_{aw}$ | 2 × $\bar{P}_{aw}$ | 2 × $\bar{P}_{aw}$ |
| **SIMV** | **Initial Settings** | | |
| Rate | 30-60 | 30-40 | 20-40 |
| $V_T$ (mL/kg) | ~5 | ~5 | ~5 |
| PEEP (cm $H_2O$) | 5-8 | 5-8 | 6-9 |
| I-time (s) | Start at 0.3-0.4, adjust PRN based on graphics | | |
| PS (cm $H_2O$) | Start at 8-12, adjust to ~⅔ PIP for $V_T$ | | |

*HFOV*, High-frequency oscillatory ventilation; $\bar{P}_{aw}$, mean airway pressure; $\Delta P$, change in pressure (amplitude); *SIMV*, synchronized intermittent mandatory ventilation; $V_T$, tidal volume; *PEEP*, positive end-expiratory pressure; *PRN*, as needed; *PS*, pressure support; *PIP*, peak inspiratory pressure.

## TABLE 23-7 Recommended Adjustments for High-Frequency Oscillatory Ventilation by Ventilator Parameter Based on Oxygen Requirements and Ventilation

| Parameter | Adjustment |
|---|---|
| Rate | Typically no change in frequency except:<br>↓ if $\Delta P > 2\text{-}3 \times \bar{P}_{aw}$ ↑ if $\Delta P < \bar{P}_{aw}$ |
| $\bar{P}_{aw}$ (cm $H_2O$) | Increase/decrease as follows based on $FiO_2$:<br>↑ by 2-3 if $FiO_2$ >50%<br>↑ by 1-2 if $FiO_2$ 25%-50%<br>No change or ↓ by 1 if $FiO_2$ <25%<br>↓ by 2-3 after surfactant therapy |
| $\Delta P$ | Increase/decrease based on $P_{CO_2}$ or $TcP_{CO_2}$:<br>↑ 5-10 if $P_{CO_2}$ >65 mm Hg<br>↑ 2-5 if $P_{CO_2}$ 55-65 mm Hg<br>↓ 2-5 if $P_{CO_2}$ 35-45 mm Hg<br>↓ 5-10 if $P_{CO_2}$ <35 mm Hg |

$\Delta P$, Change in pressure (amplitude); $\bar{P}_{aw}$, mean airway pressure; $FiO_2$, fraction of inspired oxygen; $P_{CO_2}$, partial pressure of carbon dioxide (capillary or arterial); $TcP_{CO_2}$, partial pressure of transcutaneous carbon dioxide.

**TABLE 23-8 Recommended Adjustments for Volume-Targeted Synchronized Intermittent Mandatory Ventilation by Ventilator Parameter Based on Oxygen Requirements and Ventilation**

| Parameter | Adjustment |
|---|---|
| Rate | Wean rate as tolerated for $P_{CO_2}$ <50 |
| | Minimum SIMV rate 15-20 |
| $V_T$ (mL/kg) | Wean as indicated for $P_{CO_2}$ <50 |
| | Do not wean off $V_T$ <4 mL/kg |
| PEEP (cm $H_2O$) | Wean as indicated when $FiO_2$ <0.25 |
| | Follow lung inflation by CXR |
| | Typically do not wean off <5 cm $H_2O$ |
| I-time (s) | Typically do not adjust |
| PS (cm $H_2O$) | Wean as indicated based on PIP for $V_T$ |
| | Change to tube compensation if <5 cm $H_2O$ |

*$V_T$*, Tidal volume; *$P_{CO_2}$*, partial pressure of carbon dioxide (capillary or arterial); *PEEP*, positive end-expiratory pressure; *CXR*, chest radiograph; *PS*, pressure support; *PIP*, peak inspiratory pressure; *SIMV*, synchronized intermittent mandatory ventilation.

all modes of mechanical ventilation (Table 23-8); (2) encouragement of active weaning by respiratory therapists as well as physicians and nurse practitioners; (3) written extubation criteria from both conventional ventilation and HFOV; (4) a policy that mandates daily assessment during clinical rounds of whether the infant meets extubation criteria; and (5) promotion of all approaches to noninvasive respiratory support. With this approach we have demonstrated a quality improvement process by which almost 90% of infants who meet criteria can be extubated within 24 hours of doing so, with an overall reduction in ventilator days by 40% and a median duration of mechanical ventilation of <1 day for infants of >27 weeks' gestation.

### Evidence-Based Recommendations

The best evidence base for management of RDS includes initial management with noninvasive modes of respiratory support and, for those infants requiring intubation, surfactant replacement therapy.[6,32] There is also good evidence to support the use of a volume-targeted rather than pressure-limited approach to conventional mechanical ventilation.[30] Although there is evidence to support the use of a "lung-protective" approach to mechanical ventilation in adults with RDS,[33] such trials do not exist (and probably would not be undertaken) for neonatal RDS.[17,18] Although we preferentially employ HFOV in the management of neonatal RDS, there is no convincing evidence from randomized controlled trials (RCTs) in the era of surfactant availability and advanced conventional techniques that HFOV using an "open-lung" approach results in improved outcomes compared to lung-protective, volume-targeted approaches via conventional mechanical ventilators.[15]

### Gaps in Knowledge

Despite over 50 years of experience with mechanical ventilation in the support of neonates with RDS, there remain important gaps in our knowledge. One of the most important needs is the extension of pulmonary follow-up studies beyond the first few years of life. There is now compelling evidence, primarily from pre-surfactant survivors, that altered lung growth and function may persist into early adulthood, with the potential to result in significant functional issues as the lung undergoes normal age-related declines in physiologic function.[34] Some studies have suggested that the use of much later functional assessments, rather than the short-term definitions of BPD, supports the early, sustained use of HFOV over more conventional modes of ventilation.[35-37] Nonetheless, at this time there is no clear evidence to that effect, and, when properly employed, one approach cannot be clearly advocated over the other. Additional studies are also needed to evaluate the potential benefits or harms of newer approaches to mechanical ventilator support for neonatal RDS, such as neurally adjusted ventilator assist,[38] and the use of different approaches to early noninvasive support, including high-amplitude bubble CPAP and high-frequency nasal ventilation.[39,40]

## MECONIUM ASPIRATION SYNDROME

Although meconium-stained amniotic fluid is a relatively common occurrence, particularly as gestation increases beyond 40 weeks, true meconium aspiration syndrome, or MAS, is relatively infrequent and appears to be decreasing in frequency over the past few decades.[41-44] Despite its relatively low incidence, approximately 50% of infants diagnosed with MAS may require ventilator support.[45-47]

### Key Pathophysiologic Features

MAS has a complex, multifactorial pathophysiology that is primarily inflammatory, with a variable obstructive component.[41,42,48,49,50] Key features include altered surfactant metabolism/function, obstruction of the airways, and increased pulmonary vascular resistance and/or reactivity (Fig. 23-1). These components lead to disordered surfactant metabolism and function, epithelial and endothelial membrane injury, and partial or complete obstruction of large and small airways, superimposed on an altered pulmonary vascular bed related to both inflammation and prenatal/postnatal hypoxia–ischemia. Perhaps more than any other neonatal disorder, the clinical features of MAS may be quite variable from one infant to the next and can change fairly rapidly during the course of caring for a single infant. As such, the ventilatory approach must be individualized and frequently assessed based on the predominant pathophysiology at the time. Clinical examination, radiographic features, and echocardiography may all play a role in determining the variable dominant pathophysiologic processes. This section will focus on the ventilatory approach to MAS; other adjunctive therapies may also be indicated, including surfactant replacement, antibiotics, vasodilator use, and antiinflammatory treatments, but will not be discussed in detail.

#### Surfactant Dysfunction

Disturbances in surfactant metabolism and function lead to decreased compliance of distal airspaces leading to atelectasis and intrapulmonary shunt.[49,51-53] From the perspective of ventilator management, the primary goal is attempting to establish an optimal functional residual volume through recruitment and maintenance of poorly inflated airspaces while attempting to minimize overinflation of unaffected regions of the lung and those areas where airway obstruction predisposes to air trapping. Beyond the use of surfactant replacement therapy in an effort to improve lung compliance, lung inflation is optimized through judicious application of PEEP and/or $\bar{P}_{aw}$.

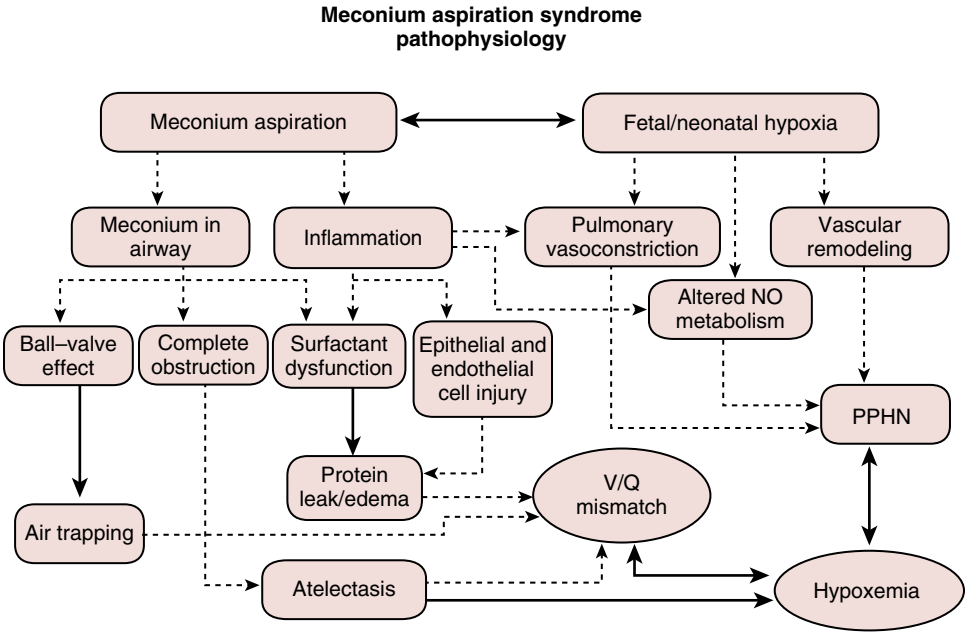


**FIG 23-1** Pathophysiology of meconium aspiration syndrome. *NO*, Nitric oxide; *PPHN*, persistent pulmonary hypertension of newborn; *V/Q*, ventilation-perfusion.

## Airway Resistance

Severe MAS is often accompanied by elevated airway resistance due to obstruction from inhaled/aspirated meconium.[42,54] In animal models of MAS, there is an early acute phase of near-complete obstruction of the large airways, followed by movement of the meconium into smaller more distal airways.[48,55] Given that the prenatal conditions that typically predispose to MAS are extant well before delivery, the vast majority of neonates with significant MAS have already moved the bulk of any inhaled meconium into the distal airways/airspaces.[41] Typically, aspiration of meconium results in overall increased lung resistance. Given the small diameter of more distal airways, the potential exists for partial or complete obstruction, or a "ball–valve" effect (Fig. 23-2). The former prevents gas from getting into the distal gas-exchange space, leading to atelectasis; the latter allows some gas into the distal airspace but impedes gas from escaping during the exhalation phase, leading to air trapping and overinflation. Saccular overinflation not only directly impairs gas exchange but can also further aggravate oxygenation through compressive effects on the pulmonary microvasculature. It is this combination of disturbed airway mechanics coupled with surfactant dysfunction creating a nonhomogeneous lung disease that makes severe MAS so difficult to manage.

## Pulmonary Hypertension

Unlike most other neonatal lung disorders, pulmonary hypertension is a common and significant problem in infants with severe MAS.[56-58] Fetal hypoxemia and inflammation are thought to be primary contributors to underlying pulmonary hypertension.[48,49,58-60] Abnormalities in nitric oxide metabolism contribute to the underlying dysfunction in pulmonary vasomotor tone.[58,61,62] As noted previously, air trapping and compression of the pulmonary vascular bed can also contribute to pulmonary hypertension. Adjunctive therapy with inhaled nitric oxide (NO) and other pulmonary vasodilators, as well as inotropic support of the systemic vascular system, may be required for management of the pulmonary hypertension.

## Relevant Principles of Ventilation

Although we most commonly use HFOV, other approaches to high-frequency ventilation (HFV) and/or volume-targeted conventional ventilation can be used in the initial management of MAS (Tables 23-5 and 23-9). The key to management includes recognition of the predominant underlying pulmonary pathophysiology. While the majority of infants with MAS do not require ventilator support, those infants that do are usually quite ill and often have a mixed pattern of both over- and underinflated lung segments, as well as severe persistent pulmonary hypertension of the newborn (PPHN).

## High-Frequency Ventilation

With HFOV the key to success is to use a lower rate, typically 6 to 8 Hz, and to set the initial $\overline{P}_{aw}$ based on the overall pattern of lung inflation. For infants with significant air trapping we start at 6 Hz with a $\overline{P}_{aw}$ similar to that on conventional ventilation. Amplitude, or $\Delta P$, is then adjusted to generate vibration of the chest to midabdomen. This approach provides a slightly greater oscillatory $V_T$ and longer expiratory phase, both of which lead to improved ventilation. For those infants with MAS who have relatively poor lung inflation, the $\overline{P}_{aw}$ is typically started at 3 to 5 cm $H_2O$ above that on conventional ventilation. Subsequent adjustments in $\overline{P}_{aw}$ are made based on $FiO_2$ response and radiographic assessment of lung inflation. In most babies with MAS we typically adjust amplitude, not frequency, to further affect ventilation. If high-frequency jet ventilation (HFJV) is employed, it is important to use a lower rate (in the range of 240 to 360 cycles per minute) as exhalation is passive and air trapping is a significant risk if the rate is too high. On occasion it may be helpful to minimally increase the inspiratory time (I-time) (from 0.02 to 0.03 seconds) to gain increased $V_T$ with high-frequency pulses. When employing HFJV, a backup rate

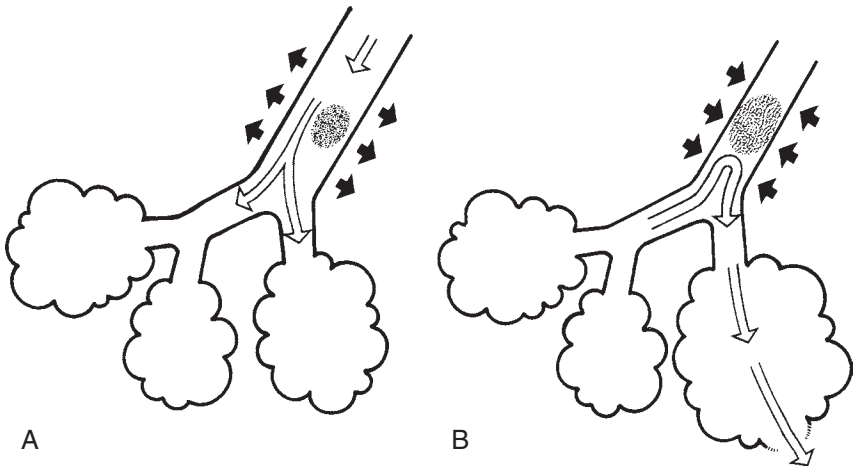


**FIG 23-2** Partial "ball–valve" air trapping behind particulate matter (i.e., meconium) in an airway, which leads to alveolar overexpansion and rupture. (**A**) Tidal gas passes beyond the meconium on inspiration when the airway dilates, but (**B**) cannot exit on expiration when airways constrict. (From Goldsmith JP. Continuous positive airway pressure and conventional mechanical ventilation in the treatment of meconium aspiration syndrome. *J Perinatol.* 2008;28(suppl 3):S49-S55; used with permission.)

**TABLE 23-9 Suggested Initial Approach to Ventilator Support of Meconium Aspiration Syndrome by Ventilatory Mode and Suspected Underlying Pathophysiology**

| Ventilatory Approach | Airway Obstruction w/Gas Trapping | Alveolar Disease w/Low Lung Volumes | Pulmonary Hypertension |
|---|---|---|---|
| Pathophysiology | ↑ Resistance<br>↑ Time constant<br>↑ Lung volumes | ↓ Surfactant function<br>↓ Compliance<br>↑ V/Q mismatch | ↓ NOS<br>Hypoxemia<br>Acidosis |
| **Conventional (SIMV)** | | | |
| Pressure-controlled | PIP to move chest; lower I-time ≤30; PEEP 4-6 cm $H_2O$; PS ~⅔ set PIP | Surfactant therapy; monitor lung volume; higher PEEP as needed to maintain EELV | iNO; $SpO_2$ 92%-98%; consider other vasodilator therapy; optimize sedation |
| Volume-targeted | $V_T$ 5-6 mL/kg; limit rate to ≤30; PEEP 4-6 cm $H_2O$; PS to achieve ~¾ set $V_T$ | Same as above | Same as above |
| **High Frequency** | | | |
| Oscillatory | Hz 6-8<br>Δ*P* vibrate chest/abd | $\bar{P}_{aw}$ as needed for 9 rib lung expansion | Same as above |
| Jet | HF rate 240-360<br>May need ↑ I-time<br>Minimal/no backup rate | PEEP as needed for 9 rib lung expansion; backup rate 2-5 | Same as above |
| Flow interrupter | HF rate 240-360<br>Convective rate 6-10 | PEEP as above<br>Set convective I-time close to 1 second | Same as above |

*NOS*, Nitric oxide synthase; *V/Q*, ventilation-perfusion; *SIMV*, synchronized intermittent mandatory ventilation; *PIP*, peak inspiratory pressure; *PEEP*, positive end-expiratory pressure; *PS*, pressure support; $V_T$, tidal volume; *EELV*, end-expiratory lung volume; *iNO*, inhaled nitric oxide; $SpO_2$, oxygen saturation; Δ*P*, change in pressure (amplitude); $\bar{P}_{aw}$, mean airway pressure; *HF*, high frequency.

may be helpful if some element of lung recruitment is indicated, using $V_T$ inflations rather than large increases in PEEP. However, backup conventional sighs should be set at a relatively low frequency, typically two to five breaths per minute (bpm) (see Tables 23-5 and 23-9). On occasion we also use the Bird VDR-4 for high-frequency flow interruption. Though not as "user friendly" as other neonatal ventilators, this device can be quite effective to aid in the removal of airway secretions for infants with large amounts of airway meconium. It is important to again remember that exhalation is passive, and thus lower rates (240 to 360) should be used to minimize risk of air trapping. Typically we use convective inflations between 5 and 10 bpm and set the I-time for convective inflations close to 1 second (see Tables 23-5 and 23-9).

### Conventional Ventilation

We almost always use a volume-targeted, SIMV-based approach to conventional ventilator support (see Tables 23-5 and 23-9). The same guiding principles should be used in initiating and adjusting support as noted above. When air trapping is the

predominant pathologic problem, it is more often caused by dynamic PEEP due to insufficient expiratory time. Set PEEP should be limited (typically ≤6 cm $H_2O$) and the ventilator rate should be kept relatively low (typically ≤30 bpm), with shorter I-times to ensure adequate expiratory time to minimize gas trapping. However, because both inspiratory and expiratory time constants are prolonged, the inspiratory times must be adequate to achieve complete $V_T$ delivery. For infants in whom the predominant pathology is alveolar disease with low lung volumes due to surfactant inactivation, PEEP should initially be set at higher levels (6 to 8 cm $H_2O$) and adjusted as needed to achieve an acceptable end-expiratory lung volume. We also commonly use pressure support to assist spontaneous breaths with a goal of support between two-thirds and three-quarters the set pressure/$V_T$ of the SIMV inflations. Because the pathophysiology of MAS includes increased alveolar dead space, these infants require slightly larger $V_T$/kg than similar infants with more homogeneous lung disease.[63]

Irrespective of the ventilatory approach used, frequent clinical, radiographic, and laboratory assessments are indicated to optimize gas exchange and minimize VILI. This monitoring is even more important following surfactant therapy and during the initial 12 to 24 hours of support as the predominant pathophysiology can and does change quickly.

### Evidence-Based Recommendations

There is a very limited "evidence" base to support the multiple management schemes employed for MAS. Although numerous trials have been conducted comparing different modes of conventional ventilation, or conventional to high-frequency ventilation, in term and preterm neonates with respiratory failure, no randomized trials have specifically compared different approaches to mechanical ventilation in a population of babies limited to a diagnosis of MAS. Therefore, the use of SIMV rather than assist/control (A/C) is a matter of practice style preference, not specifically evidence based, although it could be argued that there may be greater potential for air trapping with A/C. There is increasing evidence from RCTs involving mechanically ventilated infants diagnosed with MAS related to the potential benefit of surfactant therapy (including bolus and lavage approaches)[64-66] as well as early corticosteroid therapy (including systemic and inhaled approaches).[67,68] There is evidence that HFV may improve the effectiveness of inhaled NO by promoting optimal lung inflation.[69]

### Gaps in Knowledge

Although the evidence related to the benefits of surfactant therapy is compelling, additional studies are needed to better define the optimal at-risk population, timing, and dose of this therapy. Trials of corticosteroid therapy are relatively few and small; additional trials are needed to further clarify the overall benefit to risk effect of this intervention. The complete lack of RCTs comparing different approaches to ventilatory support in babies diagnosed with MAS (such as pressure-controlled versus volume-targeted, SIMV versus A/C, conventional ventilation versus HFV, or HFOV versus HFJV) leaves a large gap in our knowledge about optimal ventilator management of this group of patients. Given the overall decreasing incidence of MAS and the relatively limited number of babies diagnosed with MAS who require mechanical ventilation, such studies may never be carried out, but at a minimum will require a multicenter approach.

**TABLE 23-10 Published "Protocols" for Management of Neonates with Congenital Diaphragmatic Hernia[70-74]**

| Ventilator Mode | | Conventional | High-Frequency Oscillation |
|---|---|---|---|
| Peak pressure/Δ*P* | | <25-26 cm $H_2O$ | 30-50 |
| PEEP | | 2-5 cm $H_2O$ | N/A |
| $\bar{P}_{aw}$ | | <12 cm $H_2O$ | 13-17 cm $H_2O$ |
| Rate | | 40-60 bpm | 10 Hz |
| I-time/I:E | | 0.30 s | 1:1 |
| $PaCO_2$ | | 45-65 mm Hg | 45-65 mm Hg |
| $PaO_2$ | Preductal | 60-80 mm Hg | 60-80 mm Hg |
| | Postductal | >30 mm Hg | >30 mm Hg |
| $SpO_2$ | Preductal | 85%-95% | 85%-95% |
| | Postductal | >70% | >70% |
| Chest radiograph | | ~8 ribs contralateral lung | ~8 ribs contralateral lung |

Δ*P*, Change in pressure (amplitude); *PEEP*, positive end-expiratory pressure; $\bar{P}_{aw}$, mean airway pressure; *I:E*, inspiratory to expiratory ratio; *$PaCO_2$*, partial pressure arterial carbon dioxide; *$PaO_2$*, partial pressure arterial oxygen; *$SpO_2$*, oxygen saturation.

## CONGENITAL DIAPHRAGMATIC HERNIA AND LUNG HYPOPLASIA DISORDERS

Congenital diaphragmatic hernia (CDH) has remained one of the most challenging and frustrating major birth defects to manage. Since 1995, a number of treatment strategies have evolved, but there have been no large RCTs targeted specifically to the postnatal management of neonates with CDH. Despite this fact, a general consensus related to a few specific management concepts has emerged (Table 23-10).[70,71] First, the existence of a specific set of guidelines targeting early neonatal care of CDH infants is associated with improved center-specific survival.[70-73] Second, despite the absence of a clear evidence base, there is general agreement that immediate surgical repair of the diaphragmatic defect is not only unnecessary but probably detrimental.[74-77] However, specific indications for optimal timing of repair remain unclear.[78,79] Third, adoption of a gentle approach to ventilator support has been associated with reported improvements in morbidity and mortality.[80-82] However, it is unclear what the best ventilation mode is to provide gentle support. It was hoped that information from a large RCT comparing initial ventilator support with high-frequency oscillation to volume-targeted conventional ventilation would help provide answers to this question.[74] However, that study was terminated early for slow enrollment and failed to identify a significant difference in CDH outcome related to the initial ventilator mode.

### Key Pathophysiologic Features

#### Lung Hypoplasia

The most obvious pathophysiologic problem for the infant with CDH is impaired lung growth, primarily due to the space-occupying effect of abdominal viscera in the thoracic cavity. It is probable that not only the volume of abdominal organ herniation, but also how early in gestation herniation occurs, compromises lung liquid formation, and developmental defects in lung morphogenesis also contribute to the severity of lung hypoplasia.[83,84] This is evidenced by the association of decreased survival as diaphragmatic defect size increases[85] and improved survival with fetal tracheal occlusion for severe lung hypoplasia based

on very low lung-to-head ratios.[86] In addition to decreased lung size, there also appear to be altered lung development and disturbances in surfactant metabolism of both the ipsilateral and the contralateral lung with CDH,[87-91] though not all investigators agree on the adverse effects of CDH on surfactant stores or metabolism.[92] The specific mechanisms for development of the diaphragmatic defect remain unclear and are beyond the scope of this chapter. The use of animal models has contributed greatly to the understanding of possible molecular and genetic factors that may be associated with CDH, and the reader is referred to other reviews for more information.[93-95]

### Pulmonary Vascular Bed

Given that angiogenesis and vasculogenesis of the pulmonary circulation and capillary network are closely linked, impaired vascular development accompanies the altered lung growth found in CDH.[96] A variety of pulmonary vascular abnormalities have been described in animal models and neonates with CDH, including impaired growth and development of pulmonary arteries and arterioles as well as increased arteriolar medial muscle thickness,[97,98] altered expression of angiogenic factors including vascular endothelial growth factor,[99-101] decreased endothelial NO synthase expression,[102,103] impaired response to NO metabolites,[104] increased expression and activity of phosphodiesterase 5,[105] and increased expression/levels of endothelin-1 and endothelin receptor A.[106,107] The effect of decreased vascular growth and impaired endothelial cell function is an impaired pulmonary vascular response at birth to inflation and oxygen. Additionally, the postnatal response to inhaled NO (iNO) also appears to be impaired.[108,109] PPHN continues to be a major contributor to the continuing relatively high mortality rate among infants with CDH, with limited improvement since 1995 despite a variety of new therapeutic approaches.[110-113]

### Cardiac Development

Often overlooked in the pathophysiology of CDH is the contribution related to impaired growth and function of the left ventricle (LV).[114-116] The severity of the LV hypoplasia correlates with the severity of the diaphragmatic defect/hernia and appears to be more significant in left-sided compared to right-sided defects.[117] Some investigators have suggested that significant LV dysfunction related to the hypoplasia contributes to postnatal PPHN through increased pulmonary venous congestion and have recommended against early iNO use to minimize this problem.[118] Despite the apparent impact of left-sided CDH on LV growth and function, and suggested treatment with a variety of vasoactive therapies, no controlled trials have been performed to determine the optimal approach for management of this problem.[110,112,119-121]

## Relevant Principles of Ventilation

Since 2005 there has been a general acceptance of using a "lung-sparing" or "gentle" approach to mechanical ventilation of neonates with CDH.[70-72,81,82] Most developed protocols initially employ conventional ventilation, with recommended ventilator settings as shown in Table 23-10. In our NICU we use HFOV as the initial mode of support for all infants with CDH (Table 23-11), an approach that has evolved since 1995.[122] Differences in our initial support parameters for HFOV compared to those established for the VICI Trial[74] include (1) we initiate HFOV with a lower $\bar{P}_{aw}$, usually 12 cm $H_2O$, and limit initial maximum $\bar{P}_{aw}$ to <16 cm $H_2O$; (2) we often start at a lower frequency, typically at 8 Hz; (3) we use an I:E ratio of 1:2 rather than 1:1; and (4) we attempt to maintain contralateral lung inflation at 9 or 10 ribs rather than 8. It is important to emphasize that there is no clear evidence that HFOV provides increased benefit (or risk) compared to HFJV or conventional mechanical ventilation, nor is there evidence to support a specific approach to HFOV, such as the one presented here, compared to that recommended in the VICI Trial. More recently others have published observational or retrospective studies describing their approaches to the initial use of HFOV in the management of neonatal CDH.[76,123-125] We typically continue support with HFOV until after repair of the diaphragm, which is most often performed in the NICU (Box 23-1).

**TABLE 23-11 Recommended Initial Ventilator Settings for Neonates with Congenital Diaphragmatic Hernia**

| | HFOV | HFJV | SIMV-A/C |
|---|---|---|---|
| $\Delta P$/PIP | 24-28 | 20-25 cm $H_2O$ | $V_T$ 4-5 mL/kg |
| Max PIP | | 30 cm $H_2O$ | ≤25 cm $H_2O$ |
| $\bar{P}_{aw}$/PEEP | 11-13 cm $H_2O$ | 11-13/6-8 cm $H_2O$ | 4-6 cm $H_2O$ |
| Max $\bar{P}_{aw}$ | ≤16 cm $H_2O$ | ≤16 cm $H_2O$ | |
| Frequency | 8-10 Hz | 360-420 bpm | 40-60 bpm |
| I:E/I-time | 1:2 | 0.02 seconds | 0.3 seconds |
| $FiO_2$ | Goal <0.50 | Goal <0.50 | Goal <0.50 |
| **$SpO_2$ Preductal** | | | |
| First hour | >80% | >80% | >80% |
| Goal | 92%-98% | 92%-98% | 92%-98% |
| "Tolerated" | >90% | >90% | >90% |
| **$PaCO_2$** | | | |
| Goal | 45-55 mm Hg | 45-55 mm Hg | 45-55 mm Hg |
| "Tolerated" | <65 mm Hg | <65 mm Hg | <65 mm Hg |
| Chest X-ray | 9-10 rib inflation contralateral lung | 9-10 rib inflation contralateral lung | 9-10 rib inflation contralateral lung |

*HFOV*, High-frequency oscillatory ventilation; *HFJV*, high-frequency jet ventilation; *SIMV*, synchronized intermittent mandatory ventilation; *A/C*, assist/control; $\Delta P$, change in pressure (amplitude); $V_T$, tidal volume; *PIP*, peak inspiratory pressure; $\bar{P}_{aw}$, mean airway pressure; *PEEP*, positive end-expiratory pressure; *I:E*, inspiratory to expiratory ratio; $FiO_2$, fraction of inspired oxygen; $SpO_2$, oxygen saturation; $PaCO_2$, partial pressure arterial carbon dioxide.

**BOX 23-1 Recommended Respiratory Support Parameters for Consideration of Operative Repair of Congenital Diaphragmatic Hernia**

Infant "stable" for at least 24 hours as follows:

- $FiO_2$ <0.50 with $SpO_2$ ≥92%
- $\bar{P}_{aw}$ <16 cm $H_2O$ and $\Delta P$ <30
- $PaCO_2$ <55 mm Hg
- PA pressures ≤2/3 systemic (TR jet <3.0 m/s)

Note: If calculated oxygenation index is consistently <7.0 for >24 hours and persistent pulmonary hypertension of the newborn is stable, survival following operative repair is >98%.

$FiO_2$, Fraction of inspired oxygen; $SpO_2$, oxygen saturation; $\bar{P}_{aw}$, mean airway pressure; $\Delta P$, change in pressure (amplitude); $PaCO_2$, partial pressure of arterial carbon dioxide; *PA*, pulmonary artery; *TR*, tricuspid regurgitation; *OI*, oxygenation index; *PPHN*, persistent pulmonary hypertension of newborn.

For infants with minimal evidence of respiratory compromise we may change to conventional ventilation using a volume-targeted approach (Table 23-11), and these more stable infants more often go to the operating room for repair. Though the use of HFJV has been reported by other investigators, most often it has been as a rescue therapy in lieu of HFOV, and the parameters employed have not been well described.[126,127] There is clinical evidence to suggest that HFJV may be the optimal approach for ventilation of babies with CDH with an ability to ventilate using small $V_T$ and lower $\overline{P}_{aw}$ while minimizing adverse cardiovascular effects.[128] Initial settings we employ for the application of HFJV to infants with CDH are shown in Table 23-11.

Irrespective of the ventilatory approach used for managing CDH, several key concepts must be kept in mind. First, the lung is small, with a functional residual capacity that may be considerably less than normal.[129] Given the effects that both atelectasis and hyperinflation have on pulmonary microvasculature and vascular resistance, careful attention must be paid to optimizing lung inflation.[130] In that regard, the $\overline{P}_{aw}$ needed to achieve optimal lung inflation may be less than that required for a normal-sized lung, even with the reported surfactant abnormalities. Second, it is considerably more difficult to determine optimal $\overline{P}_{aw}$ and lung inflation under conditions of lung hypoplasia with minimal to no surfactant dysfunction than for infants with diffuse alveolar disease. Attempting to employ the stepwise increase in $\overline{P}_{aw}$ as suggested under the RDS section is not recommended in babies with CDH as it is too easy to provide a higher $\overline{P}_{aw}$ than is necessary without any identifiable improvement in oxygenation, particularly with the underlying issue of pulmonary hypertension. An alternate, but unproven, approach is to start at a lower $\overline{P}_{aw}$ and gradually adjust upward based on radiographic lung inflation. Third, though the minute ventilation necessary to achieve eucarbia should be the same as for infants with normal lungs, use of a $V_T$ on the higher end of normal (i.e., 6 mL/kg) may have greater risk for initiating lung injury secondary to inadvertent volutrauma in hypoplastic lungs.[131] The fact that studies by Landolfo and Sharma[129,132] report relatively normal to high $V_T$ to achieve effective ventilation should not be taken to indicate that $V_T > 5$ mL/kg ought to be employed in babies with CDH. It is unclear, however, whether higher rates (i.e., 60 bpm) and lower $V_T$ (4 mL/kg) or higher $V_T$ (6 mL/kg) at lower rates has any difference in short- or long-term outcomes for CDH. However, given the decreased complement of alveoli in this condition, physiologic $V_T$ of 5 mL/kg would probably result in volutrauma, as this volume is directed into a fraction of the normal number of terminal airspace units; this reality provides a sound physiologic rationale for the use of HFV in infants with CDH.[132] In this context it is also important to note that those infants with the greatest degree of lung hypoplasia have increased dead space-to-$V_T$ ratios, suggesting that more of the applied $V_T$ is lost as ineffective dead space ventilation.[133] Last, oxygenation is dependent as much on the impaired pulmonary vascular bed as it is on relative lung volumes. Adjustments in ventilator support must be made with the recognition that altered oxygenation could be due to increased pulmonary vascular resistance related to factors other than changes in ventilator support.

### Pulmonary Hypertension

The management of pulmonary hypertension in lung hypoplasia disorders remains controversial.[110,112,113] There are no large RCTs demonstrating short- or long-term benefit for many of the approaches that have been used, including iNO[108,110-113] (Table 23-12).[119,134-141] The reader is referred to Chapters 32 and 33 of this book and to review articles for a more thorough discussion of therapeutic approaches to PPHN.[58,111,118,134] As previously noted, a critical component of PPHN management in all neonatal lung conditions includes optimization of lung inflation.[25,122,128,130,142] Currently, there is no proven clinical approach to such lung optimization for infants with lung hypoplasia/CDH. The combination of clinical examination, monitoring indices of gas exchange, and serial chest radiographs is most commonly used.

**TABLE 23-12 Potential Vasodilator Therapies Considered for Management of Pulmonary Hypertension in Infants with Congenital Diaphragmatic Hernia**

| Therapy | Mechanism | Comments |
|---|---|---|
| Lung "specific" | | *No proven benefit by RCTs* |
| Inhaled NO[138] | ↑ cGMP production | Commonly used |
| Sildenafil[130] | PDE5 inhibitor; ↓ cGMP breakdown | Often used later in course |
| Inhaled PGI2[140] | ↑ cAMP production | Highly alkaline |
| "Nonspecific" | | *No proven benefit by RCTs* |
| Milrinone[141] | PDE3 inhibitor; ↓ cAMP breakdown | Vasodilator, inotrope, lusitrope |
| Intravenous PGI2[140] | ↑ cAMP production | Systemic effect; hypotension |
| Bosentan[142] | Blocks endothelin receptors | Potential hepatotoxicity |
| Norepinephrine[143] | 2× activation; ? ↑ NO production | ↑ SVR:PVR ratio |
| Vasopressin[144] | ? ↑ NO production | ↑ SVR:PVR ratio |
| Intravenous PGE1[123] | Inhibits cyclooxygenase | PDA "off-loads" RV |
| Cinaciguat[145] | ↑ cGMP; activates soluble guanylate cyclase | No use in neonates to date |

*NO*, nitric oxide; *PGI2*, prostaglandin I2 (prostacyclin); *cGMP*, cyclic guanosine monophosphate; *cAMP*, cyclic adenosine monophosphate; *RCT*, randomized controlled trial; *PDE*, phosphodiesterase; *SVR:PVR*, systemic-to-pulmonary vascular resistance; *PDA*, patent ductus arteriosus; *RV*, right ventricle; *PGE1*, prostaglandin E1.

### Evidence-Based Recommendations

There is almost no evidence base for clinical management of CDH.[70,71,112,143] The few randomized trials that have been performed, such as for "delayed operative repair,"[75] include only small numbers of infants and were done prior to the current era in which gentle ventilation is almost uniformly employed. Though a wide range of therapies are employed for management of PPHN, none of these approaches has been systematically studied in babies with CDH, and as of this writing the most recent reports suggest that anecdotal use has not been associated with improved outcomes in large study populations.[110,112,113]

### Gaps in Knowledge

Nearly all approaches to ventilatory and cardiovascular support of newborns with CDH require systematic investigation. There is a uniform consensus that gentle ventilation improves outcomes, though the optimal approach and device remain unclear. Identifying better clinical tools to determine optimal lung inflation,

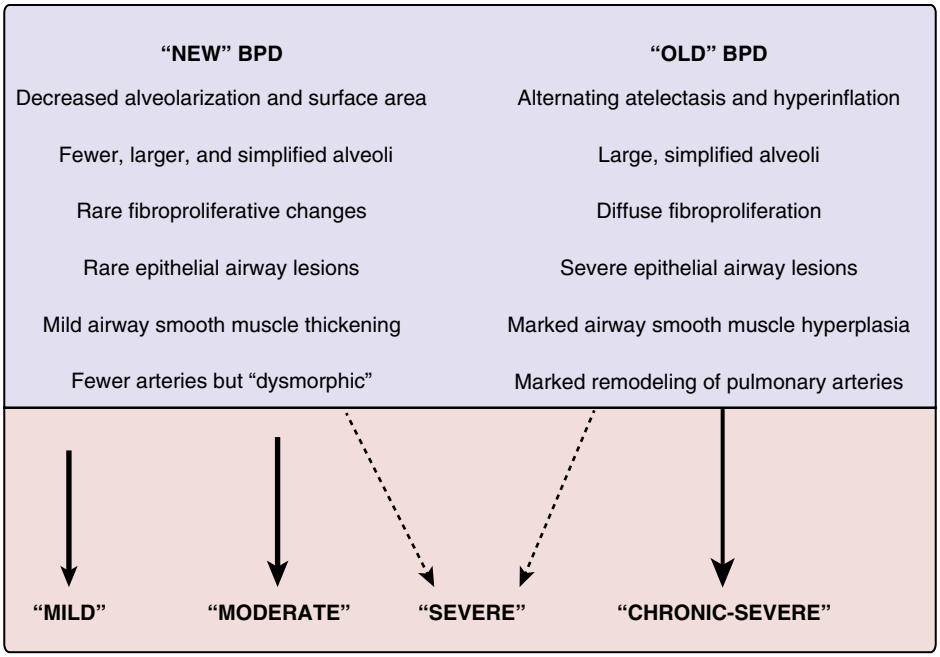


**FIG 23-3** Contrasting pathology for and relative association with definitions of bronchopulmonary dysplasia (BPD): "old" (pre-surfactant era) versus "new" (post-surfactant era).

such as the forced oscillatory technique,[25] should be investigated in babies with CDH. Another area of interest is the optimal preductal/postductal saturation to target; many centers still target a higher $SpO_2$, whereas others suggest that a lower preductal $SpO_2$ may be reasonable. Finally, in addition to postnatal studies, investigations of maternal–fetal interventions to improve lung growth and/or vascular development should be continued or developed. A number of investigations related to fetal tracheal occlusion are ongoing.[144] Animal investigations suggest that pharmacologic approaches may also be an option to improve fetal lung and vascular development in CDH.[145-147]

## BRONCHOPULMONARY DYSPLASIA*

BPD is the most common morbidity affecting surviving preterm infants, described in various studies at rates of over 40% for infants of <29 weeks' gestation.[148-151] Efforts have been made to differentiate the "old" form of BPD, first described clinically by Northway and colleagues in 1967,[152] from a "new" form of BPD suggested from human and animal studies in the 1990s[153-155] (Fig. 23-3). The epidemiology of BPD has clearly changed over time, with the vast majority of infants diagnosed with BPD now at <29 weeks and <1000 g birth weight, and most probably being of the new BPD variant with underlying impaired alveolarization.[148-151] Nonetheless, though much less common, preterm infants with an underlying pathophysiology consistent with old BPD continue to survive with severe chronic respiratory failure.[151,156] Any effort to discuss the ventilatory approach to BPD must take into consideration the wide range of clinical variability and diagnostic criteria used to make this diagnosis[155,157,158] (Table 23-13). Infants diagnosed with mild BPD may require supplemental oxygen for only the first few weeks of life, whereas infants with severe–chronic BPD continue to require positive pressure support beyond 36 to 40 weeks of postmenstrual age. These represent distinctly different ends of the BPD spectrum. Additionally, in the context of BPD care it is important to differentiate approaches aimed at prevention of BPD from the management of established severe–chronic lung disease. This section will focus on the latter group of patients, requiring ongoing ventilator support beyond the initial weeks of life and extending into the first year or beyond. Approaches designed to prevent or ameliorate BPD are discussed elsewhere in this chapter as well as in other chapters throughout this book. Also not specifically addressed in this chapter is the important concept that management of the infant with severe BPD is best served through a multidisciplinary approach to care including primary/specialized nursing and respiratory therapy support, neonatal nutritionists, and occupational/physical therapists. Additionally, other pediatric subspecialty providers may need to be members of the care team for infants with severe BPD, including pulmonology, cardiology, radiology, and otolaryngology, as well as pediatric surgery.

### Key Pathophysiologic Features

Infants with established chronic lung disease are very different from premature newborns with RDS and those with mild BPD, requiring an individualized approach based on the underlying pathophysiology of the lung (Table 23-14). Other important factors to consider in their overall management include nutritional approaches,[159] assessment for pulmonary hypertension,[160] and the possible influence of gastroesophageal reflux and aspiration on injury to the airway and lung parenchyma.[161,162]

#### Lung Pathology

Abnormalities are well described for both the airways and the gas exchange areas of the lungs (Table 23-14). The most notable

*Editor's Note: The reader is referred to Chapter 35 for a detailed discussion of the management of BPD. Although the management recommendations in both chapters are in general agreement on key principles, there is some variation in the specific recommendations, reflecting the paucity of high-quality evidence in this population.

**TABLE 23-13 Defining Bronchopulmonary Dysplasia—Modification of National Institutes of Health Consensus Conference Criteria[206]**

| Gestational Age–Birth | <32 weeks | ≥32 weeks |
|---|---|---|
| Assessment age | 36 weeks' PMA, or D/C to home | >28 but <56 days' postnatal age, or D/C to home |
| "Mild" | In room air at 36 weeks, or D/C to home | In room air by 56 days' age, or D/C to home |
| "Moderate" | $FiO_2$ >21% but <30% at 36 weeks' PMA, or D/C to home | $FiO_2$ >21% but <30% at 56 days' age, or D/C to home |
| "Severe"* | $FiO_2$ >30% ± NIV# at 36 weeks' PMA, or D/C to home | $FiO_2$ >30% ± NIV# at 56 days' age, or D/C to home |
| "Severe–chronic"* | Need for ventilator support at 36 weeks' PMA | Need for ventilator support at 56 days' age |

*The NIH Consensus Conference definition describes only "severe bronchopulmonary dysplasia"; in this table those babies continuing to require mechanical ventilator support are differentiated from those with increased $FiO_2$ need and/or other higher level noninvasive support (NIV#, positive pressure support including nasal ventilation, nasal, continuous positive airway pressure, or high-flow NC > 2 Lpm). *PMA*, Postmenstrual age; *D/C*, discharge; *$FiO_2$*, fraction of inspired oxygen; *NC*, nasal cannula.

**TABLE 23-14 Pathophysiology of the Lung in Bronchopulmonary Dysplasia**

| Respiratory Site | Issues |
|---|---|
| **Upper Airways** | |
| Glottis | Arytenoid inflammation/edema |
| Trachea | Subglottic stenosis; malacia |
| | Infection |
| Bronchus | Granuloma/stenosis |
| | Stenosis |
| | Malacia |
| Small/lower airways | Hyperplasia of epithelium and mucous glands |
| | Bronchoconstriction/increased secretions |
| | Associated vasculature |
| | Smooth muscle hypertrophy |
| | Increased reactivity/tonic constriction |
| Distal airspace | Alveolization |
| | Decreased gas exchange surface area |
| | Hypoxemia |
| | Capillary/vascular growth |
| | Impaired growth |
| | Increased vascular resistance |
| | Risk for pulmonary hypertension |
| | Heterogeneous lungs (focal atelectasis/ hyperinflation) |
| | Increased ventilation/perfusion shunt |

**TABLE 23-15 Abnormalities of Lung Function among Infants with Bronchopulmonary Dysplasia**

| Parameter | Abnormality |
|---|---|
| **Lung Volume** | |
| Overall lung volume | Decreased[166-168] |
| Functional residual volume | Decreased[169-173] |
| Compliance | Reduced[170-172] |
| Gas exchange | Impaired diffusion[164,166-168] |
| **Airway Function** | |
| Expiratory flow velocity | Decreased[168-172] |
| Resistance | Increased[170-172] |

features include interrupted alveolarization with reduced number and increased size of the remaining saccular–alveolar structures, thickened mesenchymal/septal tissues, disrupted growth and development of the pulmonary microvasculature, and varying degrees of fibrosis.[153-155,163,164] More severe changes in airway pathology, similar to that reported in pre-surfactant era old BPD, can be seen in infants requiring prolonged ventilatory support, though this appears to be relatively uncommon among infants with new BPD.[153-155,163] Additionally, infants with more severe forms of BPD may often have impaired cartilaginous development of the large and small airways, leading to tracheo/bronchomalacia.[165]

### Lung Mechanics and Function

Decreased lung volumes and alveolar surface area resulting from the interrupted alveolarization and accompanying reduced lung microvasculature lead to impaired gas exchange[164,166-168] (Table 23-15). Most studies report decreased lung compliance in infants with BPD, though this may not be sustained into later life.[169-171] Among infants with more severe forms of BPD, heterogeneous lung disease with regions of atelectasis and air trapping can also impair oxygenation owing to increased ventilation/perfusion mismatch and intrapulmonary shunts.[158] Increased resistance related to airway injury can contribute to the air trapping noted above affecting ventilation.[169-173] Failure to adjust $V_T$ owing to increased physiologic dead space also may impair gas exchange.[174]

### Relevant General Principles of Mechanical Ventilation

Even among infants with less severe forms of BPD there is increased anatomic and functional dead space. Thus, mild increases in delivered $V_T$ may be necessary to achieve reasonable ventilation goals ($Pco_2$ values in the range of 45 to 55 mm Hg for arterial samples and 50 to 65 mm Hg for capillary samples).[174] In the developing stages of BPD, beyond 7 to 14 days of age but prior to several weeks of age, the optimal approach to ventilator support is fairly similar to that recommended for the management of RDS (Table 23-5). The exception may be the above-mentioned need for some increase in $V_T$ (Table 23-16). With more chronic, severe forms of BPD, the severity of airway disease and more heterogeneous saccular–alveolar disease significantly changes the approach to ventilatory support (Table 23-16). With chronic–severe BPD even higher $V_T$ may be needed, sometimes as high as 10 to 12 mL/kg. There are several potential reasons for this: (1) similar to infants with milder forms of BPD, there is interrupted/impaired alveolarization with reduced gas exchange surface area; (2) nonheterogeneous lung disease is accompanied by increasing nonfunctional lung volume due to increased areas of atelectasis coupled with areas of overinflation (increased alveolar dead space) and (3) dilatation of the large airways due

**TABLE 23-16 Suggested Approaches to Mechanical Ventilation for Infants Diagnosed with Bronchopulmonary Dysplasia (BPD) Based on Relative Severity of BPD**

| Mild/Moderate BPD | Chronic–Severe BPD |
|---|---|
| Tidal volume ($V_T$) 5-8 mL/kg | $V_T$: May need 6-10 mL/kg due to increased dead space |
| I-time 0.35-0.45 seconds | I-time: 0.4-0.6 seconds; longer to overcome inspiratory airway resistance (?) |
| PEEP to "optimize" lung inflation | Rate: 20-30 bpm, to allow adequate lung emptying during exhalation |
| Pressure support ~¾ $V_T$ | PEEP: Quite variable; often 8-10 needed to "stent" airway open |
| Rate 20-40 based on infant effort | $SpO_2$ goals: 92%-98% |
| $SpO_2$ goals: 88%-98% based on GA | Target $PaCO_2$: 50-60 torr |
| Target $PaCO_2$: 45-60 torr | |

*PEEP*, Positive end-expiratory pressure; *$SpO_2$*, oxygen saturation; *GA*, gestational age; *$PaCO_2$*, partial pressure of arterial carbon dioxide.

to exposure to cyclic stretch from positive pressure ventilation (acquired tracheomegaly);[175] and (4) there may be loss of $V_T$ related to expansion of floppy large airways and/or to back-pressure leakage around the endotracheal tube related to high airway resistance. Increased airway resistance should be managed via longer inspiratory times to allow for more complete distribution of $V_T$. Additionally, modification of the slope of gas delivery from a square-wave form to a more bell-shaped form may also improve the flow of gas through these airways. Owing to the local and/or regional abnormalities in airway resistance and airspace compliance, a longer expiratory time is also needed for the multicompartmental BPD lung to effectively empty during the exhalation phase. Thus the combination of higher $V_T$, longer inspiratory times, and low rates (allowing for increased exhalation time) is indicated for infants who remain ventilator dependent with more chronic–severe forms of BPD. Finally, both tracheal and bronchomalacia can develop in infants with chronic–severe BPD.[165,176] For infants with these lesions, increased PEEP levels are required to prevent closure of the larger airways prior to complete exhalation of the inspired $V_T$.[177,178] At times we have used PEEP as high as 14 cm $H_2O$ to prevent airway collapse, improve expiratory airway mechanics, and reduce trapped gas lung volumes. However, the application of high PEEP must be used cautiously because of the potential to further aggravate areas of localized/regional lung overinflation. At times additional diagnostic studies may prove useful in helping to define both the severity of heterogeneous lung disease and the presence/location of significant airway lesions, including endoscopy[165,176] and dynamic high-resolution spiral CT scans.[179,180] Other evaluations that may be considered for infants with chronic–severe BPD include pulmonary function testing, an echocardiogram or cardiac catheterization to evaluate for pulmonary hypertension, and testing for gastroesophageal reflux and aspiration. In select cases we have obtained a lung biopsy to evaluate for other processes that may contribute to severe chronic lung disease of infancy.[181]

The importance of airway dysfunction in the nonventilated as well as the mechanically ventilated infant with BPD is highlighted by studies evaluating the functional and mechanical effect of helium–oxygen mixtures. The low viscosity of the helium–oxygen allows for increased laminar flow and decreased turbulent flow through obstructed airways. In the study by Migliori and colleagues, helium–oxygen was associated with decreased peak inflation pressures, increased minute ventilation, and a 50% reduction in work of breathing; additionally, improved gas exchange (partial pressure of transcutaneous oxygen ($TcPo_2$) and $TcPco_2$) was noted during both intubated and noninvasive support.[182] In a more recent study, relatively brief exposures (1 hour) to a helium–oxygen mixture again were accompanied by improvements in peak expiratory flow, dynamic compliance, exhaled $V_T$, and minute ventilation of 25% to 37%, with an associated 50% reduction in $FiO_2$ needs.[183] When the helium–oxygen mixture was discontinued, lung mechanics and $FiO_2$ needs returned to baseline values.

### Tracheostomy

Some infants with chronic–severe BPD may require tracheostomy. The reported rate of tracheostomy in populations of very preterm infants at high risk for BPD is around 3% to 5%.[156,184] The optimal time to move toward tracheostomy is unclear at this time in terms of postnatal age and/or duration of mechanical ventilation. Data from retrospective studies of large neonatal data sets suggest that most infants have been ventilator dependent for more than 2 to 3 months before tracheostomy is considered.[184,185] In our practice we tend to delay tracheostomy unless we have evidence for earlier development of trachea/bronchomalacia, but there appear to be developmental and other benefits to earlier tracheostomy. In one of these studies tracheostomy after 120 days was associated with worse neurodevelopmental outcome,[184] but this was an observational study with many potential confounders. A prospective randomized trial would be required to determine the optimal time and conditions for this serious procedure. Nonetheless, clinical practice appears to already be shifting in favor of earlier tracheostomy placement.

### Pulmonary Hypertension

Pulmonary hypertension is a relatively common problem among infants with more severe forms of BPD, with rates ranging from 20% to 50% depending on the population and approach to evaluation.[160,186,187] Mechanisms for pulmonary hypertension in this population include reduced vascular bed associated with impaired alveolarization, increased vascular smooth muscle proliferation and reactivity, and pulmonary vascular effects of localized areas of atelectasis or hyperinflation.[188] Diagnosis of pulmonary hypertension in babies with BPD requires a deliberate investigative approach. Echocardiography is the mainstay for diagnosis, but occasionally cardiac catheterization is needed for both diagnosis and evaluation of response to various therapies. Management of BPD-associated pulmonary hypertension includes adequate oxygenation (we recommend $SpO_2$ values >92%; but not hyperoxemia),[189,190] adjustment of support to prevent significant respiratory

acidosis, avoidance of lung overinflation, and occasional use of adjunctive therapies. A number of potential pulmonary vasodilators are available and in use, including iNO,[191] sildenafil,[189,192] inhaled or intravenous prostacyclin, and bosentan.[193] It is important to note, however, that no RCTs have been performed as of this writing to establish the efficacy and safety of these therapies in the treatment of infants with BPD.[190] General management of infants with severe BPD is further discussed in Chapter 35.

### Evidence-Based Recommendations

There is almost no high-quality evidence base supporting a specific approach to mechanical ventilation for infants with significant BPD. The approaches described here are based on clinical experience linked to known/suspected underlying pathophysiology. The best approach for BPD is preventing it,[194,195] but that has proved a difficult task to accomplish.[196-198]

### Gaps in Knowledge

Given the fairly broad pathophysiologic spectrum and the relatively limited number of infants with chronic–severe BPD, even large specialized centers will have difficulty in performing randomized studies targeting specific ventilatory approaches to the care of this population of infants. Multicenter approaches, such as the Neonatal Research Network, the Children's Hospital Neonatal Database collaborative,[156] and the BPD Collaborative,[199] may be able to provide large enough patient populations to perform such studies.

Though comparative effectiveness studies of treatments for severe BPD are urgently needed, research also needs to focus on interventions aimed at the prevention of BPD. Although much effort and money have been expended in the pursuit of a single "magic bullet" for the prevention of BPD, given the multifactorial pathophysiology of BPD, studies designed around "systems" approaches to preventing BPD—that is, "best demonstrated practices"[200,201]—and/or combination therapy approaches[202,203] are more likely to prove useful.

Finally, trials must be sufficiently funded to evaluate not just relatively short-term outcomes such as BPD at 36 or 40 weeks' gestation, or even at 2 to 5 years of age, but well beyond those time points. Current long-term studies, primarily of infants born prior to the uniform availability of surfactant, suggest that even preterm infants not diagnosed with BPD have reduced lung growth and impaired lung function relative to infants born at term.[14,34,204] Given the fact that lung function normally begins to decline around the end of the third decade of life, minimizing the interruption of alveolarization associated with very preterm birth, and exacerbated through processes leading to BPD should be a top research priority.[37,205]

## SUMMARY

A variety of respiratory disorders may be encountered in the neonatal period, the most common of which have been discussed in this chapter. A firm understanding of the underlying pathophysiology, and how it may change over time, is necessary to optimally apply any approach to mechanical ventilation. A variety of ventilatory modes are available, and there is limited evidence to strongly support one mode or approach over another for most of these conditions. Given the limited evidence base for much of the care we provide, there is much to be gained through controlled interventional trials within collaborative networks. It is critical to recognize that the lungs of all newborns are not developmentally complete (not just the most premature) and may be more susceptible to VILI. Protocols for weaning and extubation are strongly recommended. The most important factor associated with safe and successful ventilator management of the sick neonate is the person operating the ventilator rather than the ventilator itself.

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