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Chapter 6

Mechanical Ventilation of the Infant with Severe Bronchopulmonary Dysplasia

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Abstract

Bronchopulmonary dysplasia (BPD) is the chronic lung disease of prematurity, and is the most common morbidity associated with preterm birth. Severe BPD is defined currently as a supplemental oxygen requirement at 28 days of age and a need for >30% oxygen and/or positive pressure at 36 weeks of corrected gestational age (CGA) in an infant born at <32 weeks of gestational age. The vast majority of severe BPD is characterized by high lung resistance, such that ventilation approaches must consider the relatively long time constants needed to adequately ventilate all portions of the lung to maximize ventilation-perfusion (V/Q) matching. At the same time, any ventilation strategy must take into account the vulnerable neurodevelopmental stage that characterizes the preterm infant with severe BPD. To maximize neurodevelopmental outcomes the ventilation strategy must avoid chronic use of sedation. In this chapter, we present the physiology underlying a low-rate, high-volume ventilation approach that maximizes V/Q matching, while optimizing neurodevelopment in patients with severe BPD.

Keywords: lung resistance, time constant, neurodevelopment, preterm infant

1. Introduction

Bronchopulmonary dysplasia (BPD) was first characterized by Northway and colleagues in 1967 as a chronic lung disease afflicting premature infants after neonatal intensive care unit (NICU) treatment that included administration of oxygen and mechanical ventilation [1]. Early descriptions of BPD noted profound airway inflammation, fibrosis, areas of emphysema, and

a heterogeneous physiology. At that time BPD typically affected babies greater than 30 weeks of gestation at birth who weighed more than 1000 g, as few babies born earlier or smaller survived. As neonatal care has advanced, with widespread use of prenatal, antenatal, and postnatal treatments that have markedly improved survival, there has been a notable change in the epidemiology of BPD [2–4]. Such improvements in care include but are not limited to nearly universal administration of prenatal steroids to high risk infants, aggressive resuscitation practices, gentle forms of ventilation, improvements in parenteral and enteral nutrition, surfactant administration, and widespread use of nasal continuous positive airway pressure (nCPAP). The result of all these improvements in care has been marked increases in NICU survival of extremely low birth weight (ELBW) infants. While NICU survival has improved and BPD has become uncommon in infants greater than 30 weeks of gestation, rates of BPD have not changed for ELBW infants and thus the absolute number of infants diagnosed with BPD is likely increasing [5–7].

BPD is a phenotypically diverse disease with a variety of causes and consequences [8]. While previous definitions of BPD focused on a single diagnostic criteria (i.e., X-ray changes, a supplemental oxygen requirement at 28 days of age, or, more recently, a supplemental oxygen requirement at 36 weeks of corrected gestational age (CGA)) the most widely used current classifications divide BPD into mild, moderate, and severe based on the degree of support required at critical junctures. Mild BPD is defined as any supplemental oxygen requirement at 28 days of life, moderate BPD is defined as any supplemental oxygen requirement less than 0.3 FiO_2 at 36 weeks, while severe BPD is defined as a supplemental oxygen requirement with a FiO_2 greater than 0.3 and/or the need for positive pressure respiratory support at 36 weeks of CGA [9]. These changes in classification have been helpful in better defining BPD. However there remains a population of infants with the most severe forms of BPD who are not well characterized by the current classification and who represent the most difficult clinical cases typically cared for within neonatology (the severest of the severe). Such infants typically require chronic and extreme ventilator support with high peak inspiratory pressures (PIPs) and mean airway pressures (MAPs). They are often treated with high doses of neuroactive medications including narcotics, sedatives, and systemic corticosteroids. With a few notable exceptions [10], their neurodevelopmental outcomes are typically grim [11, 12]. The clinical management of patients with this degree of illness (informally known as "super-severe BPD") will be the focus of this chapter.

2. Disease progression and physiology

To understand the keys to clinical management of super-severe BPD as shown in the chest X-ray in **Figure 1**, it is critical to understand the underlying disease progression and physiology. ELBW infants are typically born at the intersection of the canalicular and saccular stages of lung embryogenesis whereas more mature infants in previous cohorts were born well after the saccular stage had commenced. This is a critical issue to understand modern, severe BPD because the stage of lung development during which lung damage occurs heavily influences both the pathological findings associated with the diagnosis and the clinical care required to

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manage infants with evolving BPD. Whereas older descriptions of BPD (referred to as "old BPD") typically emphasized classic progressive stages including prominent fibroproliferative changes, recent descriptions (referred to as "new BPD") have noted disruptions of distal lung growth [13, 14]. A key insight for the clinical management of the most severe forms of BPD, however, is the prominence of airway injury and dysfunction resulting from disruption of normal canalicular development.

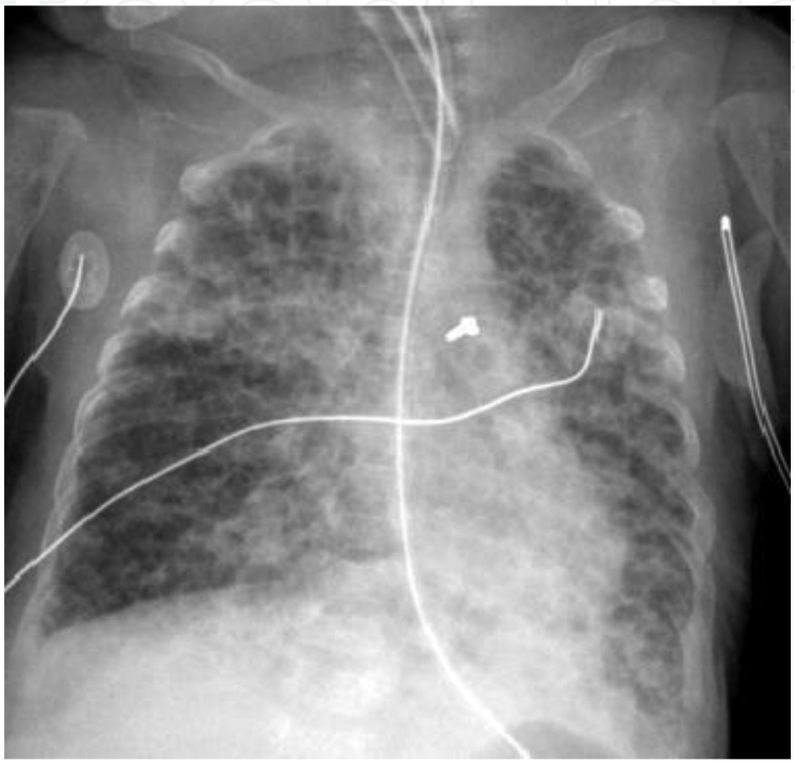

Figure 1. A typical chest X-ray for a patient with severe BPD demonstrating areas of overinflation interspersed with areas of consolidation.

Most current lung-protective strategies in neonatology are directed towards surfactant deficiency, for which extremely preterm infants are at high risk early in their NICU course [15]. Surfactant deficiency is characterized by low lung compliance (C_L, defined as change in volume for a given change in pressure or $\Delta V/\Delta P$ expressed as ml/cmH_2O) and normal lung resistance (R_L, defined as change in pressure for a given flow rate of the gas or ΔP/flow expressed as cmH_2O/ml/s). For infants in the early, acute stages of neonatal intensive care this is a very reasonable assumption, and the point of the lung protective strategy is to prevent BPD. However, this chapter discusses the mechanical ventilation of the patient with severe BPD, a relatively long time after admission to the NICU for initial respiratory care using appropriate lung protective strategies.

Let us consider how the lung fills and more importantly how the lung empties. The time needed to fill or empty is indicated by the product of C_L and R_L, termed the time constant (τ, measured in seconds). One time constant describes the time required to achieve 63% of maximal inhaled

or exhaled volume, and 5 time constants are needed for 99% of maximal inhaled or exhaled volume. Since compliance is low and resistance is normal in early, acute lung disease afflicting extremely premature infants, the time required for full inflation or deflation of the lung is very short. Thus, in order to avoid overdistention and atelectasis and consequent injury, "gentle ventilation" emphasizes high-rate, low-tidal volume ventilation administered with short inspiratory times (Ti) with adequate positive end-expiratory pressure (PEEP) *via* either conventional mechanical ventilation (CMV) or high-frequency oscillatory ventilation (HFOV). Typical "lung protective" strategies suggest CMV rates of 40–60 breaths per minute (bpm), Ti of 0.2–0.3 s and tidal volumes (Vt) of 4–6 ml/kg, and for HFOV use of the minimum MAP and amplitude (ΔP) required to achieve clinical goals. Successful application of "gentle ventilation" strategies has been associated with improvements in a number of clinical outcomes including reductions in BPD, earlier extubation, and improved survival, among others. Indeed, gentle ventilation is clearly the standard of care in early, acute lung disease in extremely preterm infants.

While it may be safe to assume that early lung disease is associated with low compliance and normal resistance and can thus be adequately managed with a high-rate, low-tidal volume approach, are these assumptions valid in well-established BPD, particularly in the most severe forms? Severe BPD is often perceived to have reduced pulmonary compliance, however the predominant findings in established BPD are complex and measurement of pulmonary physiology in infants is technically difficult. The following is a summary of the current knowledge of pulmonary function in infants with the most severe forms of BPD.

3. Pulmonary function in severe BPD

While a variety of methods have been used to assess pulmonary function in infants during tidal breathing, it is critical to understand that each method has specific limitations and the results of such measurements must be understood within this context [16]. Measurements of C_L, for instance, may be variable as they are typically determined over a limited tidal volume range and depend heavily on the lung volume at which they are obtained. Further, increased airway resistance can impact measurements of C_L during tidal breathing depending on the respiratory rate. This is termed "frequency dependence" and can lead to reductions in measured compliance even in the absence of actual changes in true compliance. Other methods of assessing resistance and compliance present different problems; the single breath occlusion technique, for instance, assumes a linear, "one-compartment" model, however evidence strongly suggests that the curvilinearity of the passive expiratory flow-volume relationship in infants with severe BPD is much better described by a "two-compartment" model. Therefore, the one-compartment analysis available in ventilator software may substantially underestimate the time constant for the damaged portions of the lungs [17–19].

Despite the limitations described above, our own data combined with those of other advanced pulmonary centers describe a fairly consistent picture. In summary, infants with the most severe forms of BPD are overwhelmingly likely to have pulmonary function that is dominated by marked increases in resistance to airflow, as demonstrated by reductions in forced expira-

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tory volume in the first 0.5 s (FEV 0.5) and in other forced expiratory flows (FEFs), with relatively normal compliance when normalized for the infant's size [20–23]. This type of pulmonary function is, in many ways, similar to that found in asthma and severe bronchiolitis and is likely the result of injury to the developing airways predominant in ELBW infants.

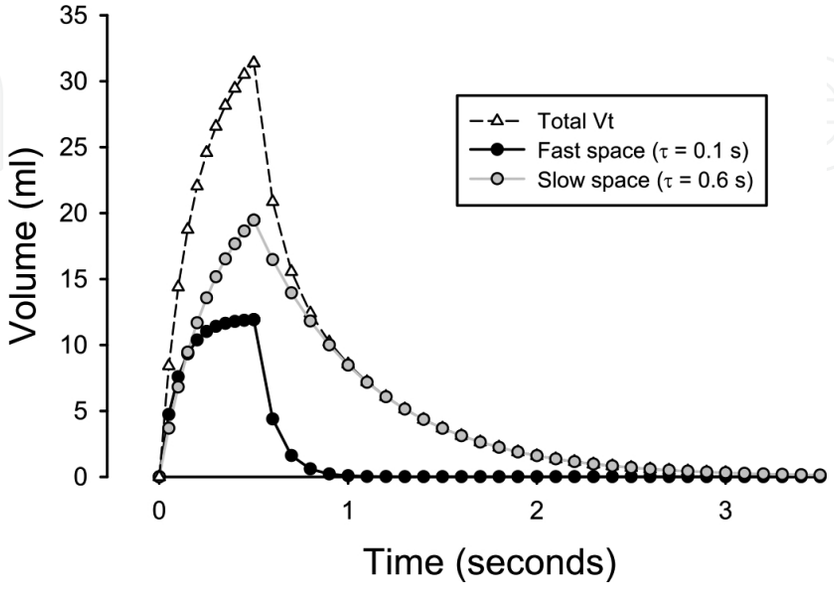

Figure 2. Volume-time curve for one breath for typical patient with severe BPD showing the fast space and the slow space. In this example, the inspiratory time is 0.5 s and the rate is 17 breaths per minute. The fast compartment (black circles) has C_L = 0.5 ml/cmH_2O, R_L = 0.2 cmH_2O/(ml/s), and τ = 0.1 s, while the slow space (gray circles) has C_L = 0.8 ml/cmH_2O, R_L = 0.75 cmH_2O/(ml/s), and τ = 0.6 s. The open triangles are the total Vt and is the sum of the volumes in the fast space and slow space. In this example the total Vt is 31.4 ml, the Vt of the fast space is 11.9 ml, and the Vt of the slow space is 19.5 ml. Clearly demonstrated is that exhalation depends entirely on the slow space as the fast space has completely emptied by 1 s, while the slow space has only completely emptied by 3.5 s, the total time for 1 breath.

The injuries to the lungs of infants with severe BPD are not regionally uniform and thus the pulmonary function of the respiratory system is heterogeneous, with some portion of the lung functioning well and other portions that are severely affected. Because of this nonuniformity, the best way to describe this heterogeneity is a "two-compartment" model with two separate and distinct sets of pulmonary mechanics [17–19]. The healthy compartment (sometimes referred to as the fast compartment) has normal or near-normal compliance and resistance, and thus a near-normal time constant. Conversely the damaged compartment (sometimes referred to as the slow compartment) is often severely injured with extremely high resistance but normal or near-normal compliance (**Figure 2**). This creates a situation in which the optimal clinical strategies necessary to achieve adequate oxygenation and ventilation will be determined by the clinician's assessment of the relative proportion of the lung that each compartment represents. Infants with relatively minimal disease, for instance, have lungs that are mostly composed of the fast compartment, while those with the most severe BPD are almost entirely slow compartment. Our own data suggest that on average 67% of the tidal volume is from the slow compartment in patients with severe BPD following bronchodilator treatment [17, 19]. This is a critical distinction as the most effective ventilatory strategy for patients with

severe BPD must take into account the slow space, and the approach to ventilating the slow space is vastly different from the approach to ventilating the normal or fast space.

In addition, infants with severe BPD have significant areas of ongoing ventilation/perfusion (V/Q) mismatch and other areas of tenuous V/Q matching which lead to ongoing hypoxia and occasional "blue spells" as the tenuous area becomes intermittently poorly ventilated.

4. Physical exam, radiological, and laboratory findings in severe BPD

Physical examination findings in infants with evolving or established severe BPD are predictable but nonspecific as they represent typical findings of respiratory distress from any cause. Patients with severe BPD are typically tachypneic and will often have retractions, grunting, and nasal flaring. On auscultation wheezing and/or rales are common findings. In addition, infants with severe BPD will often be relatively hypoxic with substantial intermittent hypoxic spells that are unpredictable and often associated with movement, coughing, gagging, or bronchospasm [18]. Such infants may further appear stressed with varying degrees of hyper- or hypotonia depending on the scale of their respiratory insufficiency. On palpation, the abdomen is typically normal; however, the liver may be displaced by pulmonary hyperinflation into the abdomen and may be easily palpable.

Radiological findings in severe BPD are typically dependent on the progression of the disease. Infants in the early stages of BPD may have diffusely hazy lungs, with marked edema, and may be underinflated. As the disease evolves and becomes dominated by resistance, however, the typical chest X-ray will demonstrate hyperinflation, with relatively little direct correlation to ventilator pressures. This more likely results from breath-stacking due to prolonged expiratory time constants rather than the set ventilator pressures. Further, as the disease progresses the chest X-ray typically becomes much more heterogeneous with areas of patchy atelectasis intermixed with areas of hyperinflation (**Figure 1**).

Laboratory findings for infants with severe BPD are typically no different than for any infant with chronic respiratory insufficiency. Most notably, many such patients will have a chronic respiratory acidosis with an elevated pCO_2 and consequently an elevated serum bicarbonate. They may have a compensatory metabolic alkalosis and if blood gases are obtained they may have a substantial base excess. In addition, infants with severe BPD are at extreme risk for growth failure and osteopenia of prematurity, and thus may have associated laboratory abnormalities including elevated alkaline phosphatase, low total protein, and low albumin levels.

5. Approach to mechanical ventilation in severe BPD

There are three critical components to successfully ventilating infants with BPD. The first is that the physician must come to terms with the fact that infants with severe BPD have significantly damaged lungs that are physiologically relatively static, in other words they have

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a chronic illness and not an acute illness. It is simply impossible for the lung function of such infants to change substantially over short periods of time (days to weeks) and it is therefore unreasonable to expect that the required respiratory support can be weaned relatively rapidly. Second, severe BPD is evolving in infants during periods of incredibly rapid neurodevelopment. Overall growth during the first few months of an extremely preterm infant's life is geometric and represents their most rapid period of growth; consequently, missed opportunities for developmental gains may be irrecoverable. Thus it is imperative that the respiratory support provided such infants be adequate to support normal interactions with their parents, family, and environment, even if requiring mechanical ventilation. Finally, the modes of ventilation used in these patients must be optimized to address the pulmonary function present in the damaged part of the lung, which likely represents the majority of the lung. Strategies that are not aimed at the diseased compartment of the lung will by definition be focused on the little remaining healthy tissue which then must compensate by absorbing the entire ventilatory load.

Since pulmonary function in infants with severe BPD is dominated by increased resistance, the expiratory time constant is very long. In infants with the most severe forms of BPD, this time constant may be as long as 0.5–0.75 s [19]. Complete exhalation, by definition, requires 5 time constants and thus may require as long as four or five seconds (5 x 0.5 = 2.5 s; 5 x 0.75 = 3.5 s). Thus, the respiratory rate must be set to allow for 5 expiratory time constants in patients with severe BPD. For if too high a respiratory rate is set on the ventilator, then there will be inadequate time for exhalation, and the subsequent breath will begin with the lung already partially inflated (breath stacking). This cycle will occur with every breath; the damaged portion of the lung will rapidly become hyperinflated, and will not be able to contribute meaningfully to overall minute ventilation (MV). Therefore the primary goal of ventilation in infants with severe BPD is to allow adequate time, in absolute terms, for complete emptying. If we take an example assuming an inspiratory time of 0.5 s and an expiratory time constant of 0.6 s, the minimum inhalation/exhalation cycle length consistent with full exhalation is 3.5 s (inhalation = 0.5 s, exhalation = 3 s), and the maximum rate that can be used on the ventilator would be 60 seconds divided by 3.5 seconds per cycle, or 17 bpm (see **Figure 2**). Any respiratory rate greater than 17, in this example, will result in breath stacking, hyperinflation, and insufficient ventilation of the bulk of the lung. This will lead to V/Q mismatch and hypoxemia which will manifest as an increasing oxygen requirement.

Carbon dioxide removal however depends on MV. MV is equal to the rate times the tidal volume (MV = rate x Vt). If the MV is 200–300 ml/kg/min, and we need to limit the set rate on the ventilator to 17 bpm to avoid hyperinflation and hypoxemia, then the only variable that we can impact is Vt. The equation can be rearranged to determine the necessary Vt as follows: Vt = MV/rate, and substituting our MV and rate gives 200–300/17 which equals a Vt of 12–18 ml necessary to provide an adequate MV at a rate of 17. A lower Vt than this will, by definition, results in inadequate MV. Furthermore, keep in mind that increasing the rate will prevent adequate emptying, leading to hyperinflation which will make the lung less compliant and thereby lead to a decrease in Vt. Essentially then, the practitioner has no alternative that is

consistent with both full emptying and adequate MV other than to utilize a low-rate, high-tidal volume ventilation strategy in the patient with severe BPD.

The patient with severe BPD who is ventilated with a faster rate usually manifests air hunger demonstrated by tachypnea, retractions, and "fighting" the ventilator. These patients are often given sedatives and sometimes even paralyzed to facilitate ventilation. However in patients with severe BPD on mechanical ventilation, once a physiological slow-rate, high-tidal volume ventilation strategy is employed, the patient begins breathing more normally without air hunger. These patients usually do not require sedation and should be awake and active, such that they can interact with their environment and with therapies. Thus, this physiological ventilation strategy not only improves V/Q matching in the lung but also allows the patient to maximally benefit from neurodevelopmental therapy. Using this approach we have found that neurodevelopmental outcomes for patients with severe BPD are no longer grim, but rather are quite good [10, 24].

A small number of patients with severe BPD will not respond to this mechanical ventilation strategy. When a patient with severe BPD does not respond to slow-rate, high Vt ventilation, then the practitioner must consider rare but important causes of hypoxemia and V/Q mismatch. We recommend structure-function studies in these patients because a very small percentage of patients diagnosed with severe BPD will actually have a predominantly restrictive lung disease, and therefore will respond better to lower tidal volumes and/or PEEP. Also, there are some patients who will have tracheobronchomalacia as the predominant pathology. These patients will often benefit from relatively high PEEP to "stent" open airways on expiration. Another important cause of V/Q mismatch in this population, particularly those with severe degrees of hypoxia, is pulmonary hypertension [25]. Thus, we recommend an echocardiogram in patients who do not respond to the slow-rate, high Vt strategy with a decrease in FiO_2, or in those patients who fail to subsequently wean on the mechanical ventilator. For patients with severe BPD it is prudent to follow echocardiograms while the patients are on mechanical ventilation, since they are at high risk of developing pulmonary hypertension [26].

Once adequate MV is achieved in infants with severe BPD, it is imperative to avoid the usual acute care mentality of rapid weaning, as the underlying pathophysiology will change only with growth. In other words, once adequate MV and V/Q matching is established in the patient with severe BPD, the focus should change from weaning the ventilator to providing optimal nutrition [27]. Furthermore, the infant with severe BPD at this stage must be adequately supported at all times to allow proper neurodevelopment. In fact, attempts to wean support rapidly are highly unlikely to succeed and can impede neurodevelopmental progress putting the patient at higher risk for adverse neurodevelopmental outcomes. Our approach is to determine the most optimal ventilator settings as quickly as possible and then to delay attempts at weaning until the oxygen requirement has steadily declined to less than 40%. Optimal ventilator settings are those settings that allow for weaning of FiO_2 and allow the patient to breath comfortably without evidence of air hunger. Even when these criteria are met, it is critical to assess each infant's developmental response to therapy. If therapies are well tolerated and FiO_2 is <40% then it is reasonable to try slowly weaning the ventilator. Although we are

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often successful extubating patients without any pressure weaning at all, if weaning is considered necessary then we recommend weaning Vt, either by decreasing PIP (for pressure-targeted ventilation) or decreasing set Vt (for volume-targeted ventilation). Each wean should be evaluated in terms of oxygen requirement and tolerance of therapies. If the wean does not result in an increase in oxygen need or a decreased tolerance of therapies then that wean was tolerated by the patient. If, on the other hand, the wean results in an increase in FiO_2 or poor tolerance of therapies then that wean was not tolerated and the ventilator should be turned up again to the previous settings. Once extubation criteria are met (**Table 1**) and the patient is successfully extubated, infants with severe BPD will often need prolonged noninvasive positive pressure via nCPAP, which should only be weaned once the infant is thriving on relatively low amounts of supplemental oxygen (25–30%). Obviously, these patients will likely need supplemental oxygen therapy for a relatively long time. Although it is rare in our practice to discharge patients home on mechanical ventilation or positive pressure, the majority of our patients are, i.e. patients are discharged home on supplemental discharged home on supplemental oxygen.

No airway anomalies
Thriving with FiO_2 ≤0.4 for at least 48 h
No recent escalation in respiratory support
Positive weight trend and good linear growth
Full enteral feeds
No surgery planned for at least 72 h
No ROP examination on day of extubation
No active infections
All needed extubation medications ordered
No recent extubation failures
Team consensus that the patient is ready

Table 1. Extubation criteria for infants with severe BPD.

6. Conclusions

Infants with severe BPD are at extreme risk for morbidity and mortality. The vast majority of these infants, however, has fairly predictable pulmonary mechanics, characterized by high resistance. Once these pulmonary mechanics are understood, it is usually possible to adequately ventilate these babies using a physiological, low-rate, high-tidal volume approach aimed at supporting ongoing neurodevelopment. It is imperative to adequately support these patients for a relatively long time to allow for lung growth and neurodevelopment. The

temptation to wean these patients rapidly, as we do for acutely ill patients, must be avoided to allow for optimal outcomes.

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