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REVIEW

Definition and Outpatient Management of the Very Low-Birth-Weight Infant with Bronchopulmonary Dysplasia

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ABSTRACT

Bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity, is the major cause of pulmonary disease in infants. The pathophysiology and management of BPD have evolved over the past four decades as improved neonatal intensive care unit (NICU) modalities have increased survival rates. The likelihood for developing BPD increases with the degree of prematurity and reaches 25–35% in very low-birth-weight and extremely low-birth-weight infants. BPD affects many organ systems, and infants with BPD are at increased risk for rehospitalization and numerous complications following NICU discharge. The management of BPD and medically related problems, particularly during the first 2 years of life, remains a continuing challenge for parents and healthcare providers. It is important that a multidisciplinary team consisting of the neonatologist/attending physician, primary care physician, and other specialized support staff work in concert and meet regularly to provide continuity of care and accurate patient assessments.

Keywords: Bronchopulmonary dysplasia; Chronic lung disease of prematurity; Complications; Discharge planning; Growth; Home oxygen therapy; Incidence; Nutrition; Outpatient management; Respiratory syncytial virus

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INTRODUCTION

The Origins of Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity, is the most common pulmonary complication of very preterm birth [1–3]. The likelihood of developing BPD is directly associated with preterm infants with a very low-birth-weight (VLBW), defined as infants born weighing < 1500 g, and extremely low-birth-weight (ELBW), defined as infants born weighing < 1000 g, who were

initially treated for respiratory distress syndrome [1]. The first description of BPD was in 1967 when Northway and associates published their landmark study regarding the clinical, radiologic, and pathologic changes observed in 32 neonates born after approximately 32 weeks' gestation with severe respiratory distress syndrome who were treated with prolonged artificial ventilation and high concentrations of oxygen [4]. Northway and associates coined the term, "bronchopulmonary dysplasia," to describe a syndrome of chronic lung disease that comprised four stages of progressive pulmonary sequelae, the latter of which extended beyond 1 month. Given improvements in neonatal care and higher survival rates among neonates of low birth weight since Northway's original observations nearly 45 years ago, the definition of BPD has undergone several iterations with respect to pathology, need for supplemental oxygen, radiographic changes, clinical presentation, and nomenclature (i.e., from "old" BPD to "new" BPD) [5–7]. This paper reviews outpatient management of some of the most common medical issues associated with BPD. These include promoting optimal growth and nutrition, gastroesophageal reflux and constipation, current immunization practices, prevention of viral respiratory infections, neurodevelopment, and management of chronic lung disease, including home oxygen therapy.

"Old" Versus "New" Bronchopulmonary Dysplasia

A workshop jointly organized by the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute convened in 2000 to further refine the definition of BPD and discuss the state of knowledge regarding BPD-induced lung injury, treatment interventions, and areas

Table 1 Definition of BPD: diagnostic criteria.[a] *Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Care Med. 2001;163:1723–9*

	Gestational age	
	< 32 weeks	≥ 32 weeks
Time of assessment	36 weeks postmenstrual age or discharge to home, whichever comes first	< 56 days postnatal age or discharge to home, whichever comes first
Mild BPD	Breathing room air at 36 weeks postmenstrual age or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need for < 30% oxygen at 36 weeks postmenstrual age or discharge, whichever comes first	Need for < 30% oxygen at 56 days postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥ 30% oxygen and/or positive pressure (PPV or nCPAP) at 36 weeks postmenstrual age or discharge, whichever comes first	Need for ≥ 30% oxygen and/or (PPV or nCPAP) at 56 days postnatal age or discharge, whichever comes first

[a] Maintain pulse oximetry saturation ≥ 92–95%

BPD bronchopulmonary dysplasia, *nCPAP* nasal continuous positive airway pressure treatment, *PPV* positive pressure ventilation

for future research [7]. In contrast to earlier definitions that lacked specificity, a new, more tailored definition of BPD was proposed that incorporated disease severity rankings assessed at identified time points in infants less than or greater than 32 weeks gestational age who required oxygen treatment for at least 28 days (Table 1) [7]. Excluded from the "new" definition were references to chest radiograph findings due to their subjective nature of interpretation and frequent lack of availability. Also excluded from the new diagnostic criteria were mentions of the clinical features of disease (e.g., tachypnea, retractions, and rales) as they are considered common to the overall description of BPD [7].

The epidemiology of BPD has changed considerably over the past four decades as the availability of surfactants, administration of antenatal corticosteroids, and improved ventilation techniques have reduced the incidence of severe lung injury in the more mature and heavier birth-weight neonate cohort [1, 7, 8]. The human lung undergoes maturation during five stages, each of which has distinct growth milestones at specific gestational periods [9]. The latter two stages extend from 26–28 to 32–36 weeks gestation (i.e., saccular stage), and from 32–36 weeks to term and beyond to 2 years of age (i.e., alveolar stage), and are characterized by alveolar and capillary development, respectively. The clinical profile of "new" BPD has shifted to a younger ELBW gestational age grouping of infants who have not reached term-equivalent development by 1 month of age [7, 8]. Whereas the main features of "old" BPD include profound inflammation, nonhomogeneous airway, and parenchymal disease, "new" BPD is characterized by decreased alveolar development and milder pathologic changes (Table 2) [8].

Risk Factors for Bronchopulmonary Dysplasia

Numerous factors have been associated with an increased risk for the development of BPD in susceptible neonates. With rare exceptions, BPD is preceded by the use of mechanical ventilation early in life [7]. Although VLBW/ELBW infants may not initially require ventilator assistance, it is often instituted because their extremely premature lung function and overly compliant chest wall usually results in CO_2 retention,

Table 2 Pathologic characteristics of "old" versus "new" BPD [8]

Old BPD	Altered inflation pattern: atelectasis and overinflation
	Severe airway epithelial lesions (hyperplasia, squamous metaplasia)
	Airway smooth muscle hyperplasia
	Extensive fibroproliferation
	Prominent vascular hypertensive lesions
	Decreased internal surface area and alveoli
New BPD	Decreased, large, and simplified alveoli (alveolar hypoplasia, decreased acinar complexity)
	Decreased, dysmorphic capillaries
	Variable interstitial fibroproliferation
	Less severe arterial/arteriolar vascular lesions
	Negligible airway epithelial lesions
	Variable airway smooth muscle hyperplasia

BPD bronchopulmonary dysplasia

apnea, weak inspiratory effort, pulmonary edema from patent ductus arteriosus, pneumonia, and/or respiratory distress. Women at risk of very preterm birth often have asymptomatic histologic chorioamnionitis and low-grade infection [10]. It has been hypothesized that antenatal endotoxin may compromise fetal lung development and prime the neonate for BPD following the introduction of further insults (e.g., mechanical ventilation, sepsis) [10, 11]. Other factors widely associated with the development of BPD include genetic susceptibility, extremely premature birth and VLBW, prolonged mechanical ventilation and oxygen administration, persistence of patent ductus arteriosus, vascular maldevelopment, and postnatal fluid overload [7, 12–15].

Incidence of Bronchopulmonary Dysplasia

The reported incidence of BPD has varied from one study to another, most likely as a result of differences in clinical definitions [16], demographics of patient populations, and management strategies used across studies [17]. These differences aside, the incidence of BPD is established to be inversely proportional to birth weight and gestational age [17]. A recent prospective trial conducted from October 2000–June 2002 by researchers at the National Institute of Child Health and Human Development Neonatal Research Network reported an overall incidence of BPD of 25–35% (depending on definition for BPD used to calculate incidence) among infants with a birth weight of 501–1,249 g [16]. The severity of BPD decreased as gestational age increased. These results were similar to the national incidence of BPD in 2002 of 33.7%, as analyzed from hospitalization records in the Nationwide Inpatient Sample [18]. Although the American Lung Association indicates that there are between 5,000 and 10,000 new cases of BPD each year in the USA. This is likely an underestimation of the true incidence given the National Vital Statistics birth data of 4.2 million new births in the USA in 2008, of which 1.46% consisted of ELBW infants [19] and the estimated percentage of VLBW/ELBW infants who develop BPD (i.e., 20–35%).

DISCHARGE PLANNING

Although survival rates for VLBW/ELBW children have significantly increased since BPD was first described, many of these infants face future problems with respect to neurodevelopmental outcomes and growth impairment [20]. In addition to higher rates of morbidity than full-term infants, VLBW/ELBW preterm infants experience an increased incidence of hospital readmission, especially during the first 2 years of life, which is more than twice that reported for preterm children without BPD [21–25]. These children also have greater need for outpatient services in early childhood [26]. These issues are further accentuated in VLBW/ELBW children with BPD. With these challenges in mind, discharge planning needs to begin well before the infant leaves the hospital and appropriate outpatient management strategies implemented to prevent or mitigate future health and development issues.

The discharge planning team typically consists of the treating neonatologist/pulmonary specialist; neonatal nurses; therapists with specialized expertise in nutrition, respiratory, and home healthcare; social workers; other professionals as needed; and infant's parents or primary caregiver. Certain elements are standard to any discharge program and take into consideration the physiologic status of the infant, treatment plans, tracking programs, and ability of the guardian to care for the child at home (Table 3) [27–31]. Before discharge, it is essential

Table 3 Discharge planning and home management programs [27, 29–31]

Physiologic stability	No acute respiratory exacerbations Oxygen requirement stable with no significant desaturations No clinically significant apnea/bradycardia Steady weight gain (20–30 g/day) on a simple feeding plan Medication schedule stable and reasonable for home use
Active program of parental involvement and preparation for care of the infant at home	Caregiver identified, adequate financial resources and health insurance in place, home care education and home assessment initiated well before discharge Caregivers should: Be trained in assessment of clinical status, including home oxygen management. They need to display skills in observation of signs of respiratory deterioration, such as hypoxia, pallor, cyanosis, lethargy, irritability, tachycardia, tachypnea, and poor feeding Be aware that oxygen needs may increase with illness, poor weight gain, etc. Be trained in CPR and emergency intervention, operation of any specialized equipment, basic infant care, and administration of any required medications Have adequate housing, access to telephone and transportation, emergency contact numbers identified, home oxygen, and other preterm issues in place
Arrangements for healthcare after discharge by a physician or other healthcare professional and identification of support services	Identification of a primary care physician and coordination of care with treating neonatologist/specialist Multidisciplinary team approach to include nursing visits for infant assessments, social workers, nutritionists, physical therapists, speech therapists, and occupational therapists
Organized program of tracking and surveillance to monitor growth and development, and timeline of pediatric care	Plotting of weight to height ratios Neurodevelopment follow-up for evidence of motor and cognitive developmental abnormalities, speech and language delay Monitoring for retinopathy of prematurity and hearing disorders
Infancy–4 months	Examine for strabismus, assess growth and nutrition monthly, evaluate family stress and parent–infant interaction
4–6 months	Assess growth and nutrition monthly, refer for standardized movement assessment and assessment of muscle tone and movement quality, evaluate family stress and parent-infant interaction
8–12 months	Assess growth and nutrition monthly, refer for standardized movement assessment and assessment of muscle tone and movement quality, refer to ophthalmologist for vision assessment, screen language, fine motor–adaptive and personal–social skills, evaluate family stress and parent–infant interaction
15–18 months	Assess growth and nutrition at 3-month intervals, assess family support at 3-month intervals, refer for standardized movement assessment, screen other areas of development and social interaction
2–5 years	Yearly neurodevelopment examination, continued medical supervision and coordination of patient care, psychosocial support, introduction to preschool experience
5–18 years	Ongoing developmental assessments, educational testing, continued medical supervision, psychosocial support, counseling about health dangers of smoking

CPR cardiopulmonary resuscitation

that the infant shows evidence of clinical stability and is able to accept oral feedings, maintain normal body temperature, and have sufficiently mature respiratory control. These functions are usually achieved by a corrected gestational age at or near term (> 36 weeks corrected) [32, 33], but related problems may persist for a longer period [34]. The infant should be examined for retinopathy of prematurity (ROP), undergo a hearing evaluation and metabolic screen review, and be given appropriate immunizations. Physiologic competencies should be assessed on an individual basis as they are influenced by birth weight, gestational age, and medical course. Consequently, predicting the time to hospital discharge for extremely preterm infants is difficult [35] and responsibility for the final decision regarding discharge rests with the attending physician [27].

It is essential that appropriate caregivers are identified and properly trained in issues relevant to care of the infant (Table 3) well in advance of neonatal intensive care unit (NICU) discharge. The caregivers must be aware that the infant will have special needs beyond those of term infants and should be able to recognize signs and symptoms of respiratory distress, poor feeding habits, and other relevant health problems before bringing these infants home. A balance needs to be achieved so that caregivers do not become overprotective to the point that they consider their child to be excessively vulnerable and limit their activities to explore and play with other children in an interactive environment that promotes normal psychosocial development [1]. Caring for a VLBW/ELBW infant with BPD presents unique challenges that can increase stress levels and promote anxiety and/or depression in those with poor coping skills [36, 37]. Appropriate family support systems should be identified and behavioral interventions implemented to mitigate any psychologic problems that arise [38].

After discharge, it is important that a multidisciplinary team, consisting of the neonatologist/attending physician, primary physician, and other specialized support staff, work in concert and meet regularly to provide a continuum of care and accurate patient assessments. The first follow-up visit should ideally be scheduled within 1–2 weeks after discharge with subsequent visits guided by the clinical status of the infant [28]. Activities and assessments to be monitored at prescheduled dates are included in Table 3.

Related Medical Problems

BPD is a disease that affects many major organ systems, including the heart, lungs, central nervous system, gastrointestinal tract, and kidneys. Infants and young children with BPD are at increased risk of rehospitalization and numerous complications during home management (Table 4) [1, 30]. The risk of poor outcomes, including death, in VLBW/ELBW infants is greatest for those with severe BPD, brain injury, and severe ROP [39]. The incidence of medically related problems is usually greatest during the first 2 years after discharge but can persist beyond very early childhood [40].

Results from early studies on the long-term effects of “old” BPD on pulmonary function suggested that infants with severe BPD could remain symptomatic and exhibit evidence of airway obstruction as adults [41]. Initial results from more recent studies in children with “new” BPD appear to be somewhat similar to previous findings and indicate that these children have a continuum of poor respiratory health that extends out to at least 8 years of age [42, 43]. However, longer-term pulmonary effects of “new” BPD remain to be fully studied. Impaired neurodevelopment in children with BPD, as manifested by difficulties with gross and fine

Table 4 Potential medically related issues/complications of BPD after hospital discharge [1]. *Adapted with permission from Vaucher YE. Bronchopulmonary dysplasia: an enduring challenge. Pediatr Rev. 2002;23:349–58P*

Cardiovascular system	Systemic hypertension
	Pulmonary hypertension
	Cor pulmonale
	Congestive heart failure
Respiratory system	Bacterial and viral pneumonia
	Bronchitis
	Respiratory syncytial virus
	Reactive airway disease/wheezing
	Aspiration
	Exercise intolerance
	Glottic and subglottic damage
	Tracheal and bronchial stenosis, tracheobronchomalacia
	Acute life-threatening event
	Sudden infant death syndrome
Neurologic system and development	Impaired motor and cognitive function
	Impaired social responsiveness to animate and inanimate stimulation
Feeding, nutrition, and gastrointestinal system	Slow weight gain and failure to thrive
	Vitamin and mineral deficiencies
	Feeding intolerance
	Gastroesophageal reflux
Other	Decreased renal blood flow and glomerular filtration rate
	Renal calcifications
	Osteopenia, rickets, fractures
	Hearing loss

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motor skills, impaired visuomotor integration, and comparatively lower intelligence quotient (IQ) scores and school performance than controls, is common and thought to result from multiple insults, including prolonged hypoxemia [44]. Careful attention should be given to results of standardized comprehensive testing conducted when the child enters school, as the most significant neurodevelopment issues secondary to BPD may first become evident at this time [30]. Other potential medically related issues in children with BPD include impaired growth and diminished fat stores [45]; respiratory infection, especially with respiratory syncytial virus (RSV) [46]; gastroesophageal reflux, which is influenced by feeding intolerance and prolonged gastric tube use [47]; sensorineural and/or conductive hearing loss [48]; and ROP.

OUTPATIENT MANAGEMENT

Growth and Nutrition

Failure to thrive is common among infants with BPD [17, 31] due to increased rates of energy expenditure, and increased nutrient and caloric requirements. Oral aversion, feeding intolerance, and/or gastroesophageal reflux all

make feeding difficult. Poor weight gain may also be a sign of unsuspected hypoxia, especially at night when oxygen saturations fall during sleep. Consequently, infants with BPD do not always achieve reference growth during their first year despite nutrition plans that include protein and energy intake comparable with those recommended for healthy term infants [49]. During early childhood, VLBW/ELBW children continue to be smaller and lighter than their normal weight counterparts, with catch-up growth usually occurring between 8 and 14 years of age. As such, growth monitoring is an integral part of the medical and nutritional assessment of these infants because of the effect of poor nutrition on the developing brain [50] and potential cognitive, neurologic, and neurosensory morbidity [51].

The goal should be to attain comparable growth velocities and percentiles for corrected age as with those for term infants [17]. At 40 weeks corrected age, growth assessments for infants with BPD should be plotted on standard charts that take into consideration length, weight, length/weight ratio, and head circumference. These should be plotted using the infant's corrected age. Each of these measurements has a prognostic ability for assessing appropriate growth. Optimal weight gain targets are 20–30 g/day with emphasis on the rate of weight gain. Small head circumference at 1 year is linked with low cognition and learning disabilities at school age [52]. Head circumference should fall within 1 SD for corrected age and infants with head circumference that is ≥ 2 SD less than the mean should be closely watched for developmental delays. Optimal growth targets are 0.7–1.1 cm/week for linear growth and 0.4–0.6 cm/week for head circumference growth. Infants who are not on a growth trajectory that is at least parallel to standard curves deserve further evaluation.

The basic caloric and protein requirements of the infant with BPD frequently exceed those of the term neonate. Caloric and protein intake in VLBW/ELBW infants may need to be increased because of the higher metabolic needs. Caloric and protein supplementation presents unique challenges, and postdischarge nutrient requirements for the preterm infant are constantly undergoing revision. Current recommendations are designed to provide nutrition to approximate the rate of growth and weight gain for a normal fetus of the same postmenstrual age [53]. Standard formula may be carefully fortified up to as high as 27 cal/30 mL by following guidelines, such as those provided by the Children's Hospitals and Clinics of Minnesota [54]. Currently available specialized premature formulas (3.0 g per 100 kcal) and postdischarge formulas (2.8 g per 100 kcal) contain significantly more protein than the standard formula. A study in 18 healthy VLBW infants compared the effects of giving isocaloric formulas containing either 3.6 g of protein per 100 kcal versus the standard 3.0 g per 100 kcal. In both formulas, the protein was provided as fully hydrolyzed bovine whey protein. The high-protein group showed greater nitrogen balance and weight gain without any evidence of uremia or metabolic acidosis [55, 56].

Breast milk feeding has been encouraged for VLBW/ELBW infants as it may help prevent future cognitive problems and offers other health benefits. If the mother breast feeds, individualized fortification of expressed milk may be required to ensure the infant receives much-needed nutrients and calories not contained in the milk. Preliminary data from a limited number of studies indicate that nutrient-enriched mother's milk improved cognitive development among very preterm infants [57], but significant effects on growth parameters were equivocal [58, 59]. Careful monitoring should be performed with the help of a professional experienced in this area.

Attention should also be given to the vitamin, folate, mineral, iron, and trace element needs

of the infant and appropriate supplementation provided. In addition to correcting any deficits, vitamin and mineral supplementation may also aid in recovery from BPD [17]. VLBW/ELBW infants are at high risk of anemia because they have low iron stores, which are depleted quickly. Elemental iron supplementation should start early on (usually between 4 and 8 weeks) at a dose of 2–4 mg/kg per day and continued for 12–15 months [60]. However, additional iron supplementation (up to 6 mg/kg per day) may be required for some VLBW/ELBW children.

Gastroesophageal Reflux and Constipation

Reflux is a common disorder in the VLBW/ELBW infant with BPD [61]. Symptoms of severe reflux may include feeding aversion, failure to thrive, or worsening of chronic lung disease. Mild reflux may be treated by thickening feedings with rice cereal, maintaining the infant in a 30° prone position (with observation) for approximately an hour after feeds, and use of a pacifier. Medication and occasionally surgery may be required for severe gastroesophageal reflux. Constipation is very common in formula-fed infants due to a combination of factors, including high caloric formula feeds and insufficient fluid intake. For cases of severe refractory constipation, alternative causes should be sought, such as an undiagnosed stricture from previous necrotizing enterocolitis.

Immunization

The American Academy of Pediatrics notes that most preterm infants, including those with BPD, produce sufficient disease-preventable immunologic responses and are not at significantly increased risk for adverse events following full-dose vaccine administration [62]. Preterm infants should, therefore, receive the standard childhood vaccines consistent with their chronologic age. As all preterm infants are at increased risk for complications due to influenza, they should be administered influenza vaccine beginning at 6 months of age and according to recommendations and dosing schedules established by the Advisory Committee on Immunization Practices [63]. It is also recommended that all members of the household > 6 months of age be vaccinated against influenza [63].

Viral Respiratory Illness

In the USA, bronchiolitis secondary to RSV infection is the leading cause of hospitalization due to serious lower respiratory tract disease in infants and young children [64]. The combined presence of BPD and premature birth increases the likelihood of hospitalization due to RSV illness, especially in infants and children younger than 24 months [65]. A good plan to be practiced by caregivers to reduce the likelihood for infections includes meticulous hand washing; avoidance of large crowds, such as those present in shopping malls, daycare centers, and physician waiting rooms; and postponement of any infant elective surgeries until after the respiratory season. No vaccines against RSV are presently available, but a monoclonal antibody that affords passive immunity against serious lower respiratory tract RSV illness is available for specified high-risk populations [66].

Medications

The treatment of BPD can be categorized into three distinct stages that include prevention (stage 1, up to 7 days postnatal), treatment of evolving BPD (stage 2, beginning at 7–14 days of age), and treatment of established BPD (stage 3,

beginning at 28±7 days of age) [67]. Medications used during outpatient management of infants with BPD (i.e., stage 3) include corticosteroids, bronchodilators, and, rarely, diuretics [1, 67].

Systemic corticosteroids should be used with caution, particularly in the newborn period, as the benefit of reduced mortality needs to be weighed against the risks of serious short-term safety concerns and potential for neurodevelopmental impairment [68]. Inhaled corticosteroids are routinely used for treatment of asthma-like symptoms in these children, but few studies have documented their clinical effectiveness for routine outpatient management or improvement of BPD [1, 69]. Inhaled bronchodilators (i.e., beta$_2$-agonists, anticholinergic agents) can improve short-term lung function by decreasing airways resistance in infants with BPD who have hyperactive airways. The etiology of wheezing in children with BPD is different from true asthma, and few studies have evaluated the efficacy of bronchodilators in patients with stable BPD beyond the neonatal period [70]. Routine administration of bronchodilators to stable outpatients with chronic lung disease is not warranted and should be reserved for children with clinical or functional evidence of reversible airways obstruction [2, 71]. The preferred method of bronchodilator delivery in this population is by metered-dose inhaler, with or without a spacer device and facemask, as it results in greater lung deposition than that achieved with nebulization [69]. Thiazide diuretics and spironolactone mobilize excess fluid and improve lung compliance acutely but their use in long-term outpatient management should be reserved for children with impaired cardiac function [1, 2, 71]. Pulmonary compliance, lung function, and hyperreactivity with wheezing usually improve over the first 2 years of life. However, overall reduced respiratory reserve may persist in a latent fashion and increase the risk of a chronic obstructive pulmonary disease-like illness later in life [2].

Home Oxygen Therapy

The goal of successful home oxygen therapy is to promote growth and repair of the developing lung, improve exercise tolerance, optimize cognitive development, and reduce the risk for pulmonary hypertension [1]. An added benefit of oxygen therapy may also be promotion of weight gain [72]. These positive effects are due to the ability of oxygen to reduce pulmonary artery pressure, acutely reverse functional hypoxic vasoconstriction, and decrease metabolism [1, 73]. Controversy still exists regarding the specific criteria for use of home oxygen therapy for infants with BPD despite over 20 years of use, as well as its impact on patient outcome. Results of a retrospective study of neonates born at a median gestational age of 27 weeks indicated that children with BPD who required home oxygen therapy after primary hospital discharge had increased respiratory morbidity and greater healthcare resource utilization during the first 2–4 years of life than similarly matched children who did not require home oxygen therapy [74]. The home oxygen cohort experienced significantly more outpatient attendances, visits to specialists, prescriptions, and total healthcare costs than the comparator group, even though most were no longer dependent on oxygen use. A greater proportion of the home oxygen group experienced wheezing in general, more frequent wheezing than children with wheezing in the comparator group, and required inhaler therapy. Further trials are necessary to determine whether these findings are the results of a more severe disease among children who required home oxygen therapy. For a successful home oxygen program, careful selection and education of the family/caregivers and meticulous follow-up with the interdisciplinary healthcare team are essential [75]. Weaning from oxygen therapy is a slow process that involves close management to avoid potential complications,

and should only be attempted after the infant is clinically stable and shows signs of adequate weight gain [29]. One such weaning program is described in Table 5 [1, 17, 29]. Persistently low oxygen saturations resulting from too rapid oxygen reduction or discontinuation may result in poor sleeping and feeding, poor weight gain, and developmental delays [72, 73]. After the infant is completely weaned from oxygen therapy, monitoring of respiratory status and weight gain should continue for up to 6 months or more. To reduce concern, parents should be informed that reinstatement of oxygen support therapy may be necessary, especially during the winter season when viral respiratory infection is common [1, 29].

The American Thoracic Society currently recommends that infants with BPD who are past the age of oxygen-induced ROP should be supplemented with oxygen to maintain an oxygen saturation of ≥ 95%, including during feeding and sleep [1]. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) and Benefits of Oxygen Saturation Targeting (BOOST) trials suggest that lower oxygen saturation targets may be of benefit, and may reduce the overall burden of home oxygen therapy [76, 77]. Halbower and McGrath accurately conclude that, "a consensus for the optimal oxygen saturation target in infants with chronic lung disease is essential. Future research efforts should emphasize oxygen saturation goals that optimize [growth and] development while simultaneously avoiding collateral damage to vulnerable organs" [78].

Neurodevelopment

BPD poses a significant risk for neurodevelopmental compromise. Postnatal infection and/or sepsis, periventricular leukomalacia, severe intraventricular hemorrhage, hearing impairment, and severe ROP are all important confounding variables that can greatly affect an infant's neurodevelopmental outcome. The risk of neurodevelopmental impairment, cerebral palsy, and low IQ more than doubled in infants with severe BPD compared with infants with mild BPD. In a longitudinal study of motor and mental outcomes at 3 years of age, children with BPD of low socioeconomic status and minority race also appeared to have poorer cognitive outcomes [79]. In contrast, socioeconomic status does not appear to

Table 5 Monitoring of home oxygen therapy for BPD [1, 17, 29]

Monitor for signs of hypoxia (e.g., cyanosis, lethargy, tachycardia, and irritability), poor weight gain, intercurrent illness
When possible, oxygen saturations should be evaluated while awake and asleep and during feedings
Wean slowly over several months and do not wean during intercurrent illness, as this is a time when oxygen requirements may increase • Wean by small, incremental reductions in oxygen flow rates such as progressive halving of flow rates (e.g., from 0.5–0.25 to 0.125–0.0625 L/min) • Weaning should begin during daytime hours when the infant is awake and alert, for a period of 1–2 hours. High saturation targets > 97% are indicative of oxygen saturation, > 92% while asleep • Observe infant for 2–4 weeks before next oxygen decrease • Night-time weaning should begin after a minimum of 1 month of no daytime oxygen
Consider continuation or reinstatement of night-time oxygen if inadequate weight gain or new signs of hypoxia are evident

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affect motor outcome positively or negatively [79]. These findings underscore the need for early diagnosis and intervention, and investigation into the potential role of BPD in higher rates of learning disabilities in VLBW/ELBW infants that may extend into the early school age period and beyond.

CONCLUSION

The pathophysiology and management of the VLBW/ELBW infant with BPD have evolved over the past four decades as improved NICU modalities have increased survival rates. However, the management of BPD and medically related problems, particularly during the first 2 years of life, remains a continuing challenge for parents and healthcare providers. The following quote written by Dr. Mildred Stahlman, who is credited with the development of the modern NICU, appeared more than 20 years ago but is still relevant and applicable to current BPD management issues: "As sanguine as the future looks for [surfactant] therapy, it may leave us with more VLBW infants who survive where potential for normal growth and development is unknown, and whose very immature organ systems, besides the lung, are still susceptible to metabolic, neurologic, and other problems" [80]. There are many questions left to be answered by additional research on the effects of current and future treatment modalities on the long-term prognosis in these children.

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