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PRACE POGLĄDOWE

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Current Aspects of the Bronchopulmonary Dysplasia Problem in Newborns

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Bronchopulmonary dysplasia (BPD) remains important cause of morbidity of very premature infants significantly affecting their long-term outcomes. Despite the all developments and latest advances in perinatal medicine the incidence of BPD has not decreased much during the last decades. Significant changes in BPD definition, pathology, pathophysiology, clinical course, radiological findings and management have occurred over the last 40 years. After many years of intensive and extensive investigations aimed to study mechanisms of BPD development and elaborate effective methods of its prevention and treatment, there is a discouraging paucity of proven safe and beneficial therapies to prevent or limit the severity of BPD. Additional studies of respiratory technologies, management strategies, and protective molecules are needed.

Key words: *bronchopulmonary dysplasia; definition; consequences; pathogenetic mechanisms; prevention; treatment; prematurity*

Aktualne aspekty problemu dysplazji oskrzelowopłucnej u noworodków

Dysplazja oskrzelowo-płucna (BPD) pozostaje ważną przyczyną śmiertelności bardzo wcześnie urodzonych noworodków, ma ona znaczne i długoterminowe skutki. Pomimo rozwoju i najnowszych postępów w medycynie prenatalnej częstotliwość występowania BPD w ostatnich dekadach nie obniżyła się. W ostatnich 40 latach nastąpiły zaś znaczne zmiany w definicji BPD, patologii, patofizjologii, obserwacji klinicznej, ukazały się także odkrycia w dziedzinie radiologii i postępowania. Po wielu latach intensywnych i rozległych poszukiwań w celu zbadania mechanizmów rozwoju BPD i opracowania szczegółowych metoda zapobiegania i leczenia tego schorzenia, jest tylko zniechęcający niedostatek sprawdzonych i korzystnych metod terapii, które jedynie zapobiegają lub zmniejszają dotkliwość BPD. Konieczne są dodatkowe badania w dziedzinie technik oddechowych, strategii postępowania i cząsteczek obronnych.

Słowa kluczowe: *dysplazja oskrzelowo-płucna, definicja, konsekwencje, mechanizmy patogenne, profilaktyka, leczenie, wcześniak*

The condition known today as bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD) of prematurity was first described by Northway in 1967 in premature infants who had severe respiratory distress syndrome (RDS) and required prolonged mechanical ventilation with high inflation pressures and inspired oxygen concentrations [1]. The mean birthweight of about 30% of infants who survived mechanical ventilation with BPD was 2200 g, and the mean gestational age was 34 weeks. Non-survivors had a mean gestational age of 31 weeks. Subsequently, Bonikos and colleagues demonstrated that oxygen exposure alone could cause many of the anatomic changes of BPD in newborn mice [2]. The pathology was characterized by abnormalities of the terminal airways, the hallmark of which was an intense interstitial fibrosis and hyperplasia

of the smooth muscle. Affected infants suffered chronic respiratory failure, with hypoxemia and hypercapnia, and many developed cor pulmonale.

Since then, advances in perinatal medicine – including major breakthroughs such as antenatal steroids and postnatal surfactant – have allowed the survival of infants that are more and more immature. However, the incidence of BPD in survivors of preterm birth has not decreased significantly because of the improved survival of large numbers of extremely low birthweight (ELBW) infants. The epidemiology of BPD has changed. With the improvements in care, factors other than mechanical ventilation and oxygen exposure contribute to the occurrence of BPD in ELBW infants, including postnatal sepsis, patent ductus arteriosus, and antenatal chorioamnionitis [3]. Some ELBW infants now develop BPD without initially having severe respiratory distress syndrome (RDS) or initially requiring much supplemental oxygen or mechanical ventilation [4].

The term "new BPD" now is being used frequently to describe a progressive lung injury syndrome first of all in ELBW infants characterized clinically by hazy lungs, minimal cystic emphysema or hyperinflation that is apparent on chest radiographs, a persistent oxygen requirement that slowly resolves, less airway reactivity, and less pulmonary hypertension (blue spells) than in the past. Infants who have died of the new BPD have minimal fibrosis or airway injury but a striking decrease in normal alveolar septation and microvascular development [5, 6]. In 2007, marking the 40th anniversary of Northway's seminal description, infants at risk for BPD are born at < 28 weeks' gestation when they are just beginning the parallel processes of alveolarisation of the distal lung saccules and development of the alveolar capillary bed [5].

DEFINITION OF BPD

The lack of uniformity in the diagnostic criteria of BPD is prevalent throughout the literature and is responsible for much of the variation in incidence of BPD between reports [7]. The different diagnostic criteria for BPD have largely been based on a single clinical sign, the need for prolonged oxygen therapy, which served as a marker for chronic respiratory failure. Most studies have used oxygen supplementation at 28 days of age [8] or at 36 weeks postmenstrual age [9] as definitions of BPD; however, both of these definitions were not accurate (≤ 63% accurate) in predicting long-term poor pulmonary or neurodevelopmental outcomes [10].

In 2000, a workshop on BPD organized by the National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the Office of Rare Diseases reviewed the current definition of BPD and developed the diagnostic criteria for BPD based on gestational age (<32 wks versus ≥32 wks) and severity (mild, moderate, or severe based on oxygen supplementation at 28 days of age and 36 weeks postmenstrual age) [11] (Table 1). A major limitation was that the criteria for oxygen requirement varied among physicians. A recently developed physiologic definition of BPD may improve the precision of the diagnosis of BPD and comparisons of its incidence among centres [12].

According to the presented criteria the current diagnosis of BPD no longer requires as its part antecedent exposures (e.g., RDS, mechanical

TABLE 1. Current Diagnostic Criteria for BPD

Gestational age (GA) at birth	**Mild** Supplemental oxygen (for 28 days) plus	**Moderate** Supplemental oxygen (for 28 days) plus	**Severe** Supplemental oxygen (for 28 days) plus
<32 wks	Room air at 36 wks corrected GA or at discharge	Need for <0,3 FiO_2 at 36 wks corrected GA or at discharge	Need for ≥ 0,3 FiO_2 ± positive pressure support at 36 wks corrected GA or at discharge
≥32 wks	Room air by postnatal day 56 or at discharge	Need for <0,3 FiO_2 by postnatal day 56 or at discharge	Need for ≥ 0,3 FiO_2 ± positive pressure support by postnatal day 56 or at discharge

Physiologic Test for Diagnosis of BPD
Infants at 35 to 37 weeks PMA receiving mechanical ventilation, continuous positive airway pressure, or >30% O_2 with saturation of <96% have BPD
Infants receiving <30% O2 or >30% O2 with saturation of >96% tested for O_2 need
– O_2 progressively decreased gradually to room air
– No BPD if saturation is >90% in room air for 30 min
Adapted from Jobe and Bancalari [11] and Walsh, et al [12], and Jobe [13].

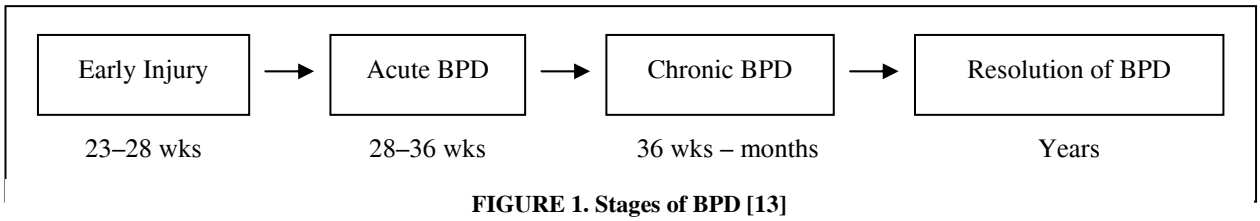

FIGURE 1. Stages of BPD [13]

ventilation), abnormalities on a chest radiograph, or any laboratory test.

The term bronchopulmonary dysplasia (BPD) best describes chronic lung disease in preterm newborns. Some term newborns can have BPD subsequent to mechanical ventilation for neonatal respiratory or other conditions different from RDS. Chronic lung disease (CLD) of prematurity sometimes is used interchangeably with BPD, but this term is best reserved for other chronic lung diseases of the preterm infant that can arise after an initial period without an oxygen or ventilatory requirement. All of these disorders are types of chronic lung disease of infancy, which can later evolve into CLD of childhood and adolescence [14]. According to Jobe [13], it is helpful to think about the stages of BPD development that are clinically relevant to developing and testing appropriate therapies (Fig. 1).

INCIDENCE OF BPD

The incidence of BPD is difficult to assess and compare because it varies widely depending on influence of several factors. First of all, there is a lack of universally accepted definition of BPD; the differences exist in patient susceptibility and management in different populations and institutions; different ways of incidence calculation may be used (number of *all* premature infants or only *surviving* premature infants within a certain weight or gestational age category or only ventilated infants etc. used as the denominator); and population at risk may be different (e.g. survival rate of ELBW infants, administration of antenatal steroids or exogenous surfactant etc.).

From the early 1980s to the early 1990s, the rate of infant mortality and BPD development among premature infants decreased. But until the end of the 1990s the incidence of BPD increased again and stabilised at the level of about 25–35%. Despite its persistence, the BPD of today has been noted to be less severe than the BPD of the past [15]. In a recent study where BPD was defined as oxygen need at 36 wks post menstrual age, the average incidence of BPD in 16 leading academic centres of USA was 42% in infants with birth weight of 501–750 g, 25% in infants with birth weight of 751–1000 g, 11% in infants with birth weight of 1001–1250 g, and 4% in infants with birth weight of 1251–1500 g [16].

Unfortunately there are no official statistical data representing the overall BPD incidence in Ukraine. 12 years data from our regional tertiary centre suggest that about 4000 infants born annually in Ukraine may have a risk of BPD development with up to 400 new cases of CLD every year.

MAIN CONSEQUENCES OF BPD

It has been pointed out that BPD and CLD are not clearly definable entities; during the course of CLD dynamic processes such as continuing injury, inflammation, healing, repair, growth, and maturation occur concurrently or sequentially in the lung. Consequently, it is difficult, if not impossible, to separate the interacting effects of prematurity, low birth weight, neonatal respiratory diseases, treatment, and subsequent respiratory illnesses. Moreover, as the diagnosis of BPD is not based on specific lung function abnormalities and the epidemiology of BPD is affected by a treatment that has been evolving over decades, the spectrum of pulmonary abnormalities and outcomes has to be heterogeneous.

There are two well-recognized consequences of BPD development. The obvious one is pulmonary. By definition, BPD infants are chronically oxygen dependent and many are discharged home on supplementary oxygen. Although they may require supplementary oxygen for many months, lung growth and remodelling results in progressive improvement of pulmonary function and few BPD patients remain oxygen dependent beyond two years of age [17].

Approximately 50% of infants with BPD require readmission to the hospital during early childhood for respiratory distress and this remains the same for the present population of BPD infants [18]. The readmission rate is highest in those infants who have had an RSV infection [19] and/or required supplementary oxygen at home [20]. Troublesome respiratory symptoms (cough

and wheeze) requiring treatment are common in children and even young adults who had classical BPD [18]. The present population of BPD patients also frequently suffer respiratory symptoms, particularly if they have had an RSV infection. In the first two years after birth, BPD children have high airways resistance, evidence of gas trapping and ventilation inhomogeneity. In the majority, lung growth and remodelling results in progressive improvement of pulmonary function [21], but airflow abnormalities may remain.

Airways obstruction, airway hyper-reactivity and hyperinflation have been demonstrated in adolescents with classical BPD [22] but the long-term outcome of children who have suffered ''new'' BPD is not known. Results of pulmonary function studies at one year of age suggest they may suffer less airflow limitation than those who had classical BPD. New BPD, however, may be associated with impaired antenatal lung growth and indeed lung volumes in such infants studied at term have been demonstrated to be lower than prematurely born infants of similar postmenstrual age without BPD [23]. Infants with new BPD require careful follow-up to determine if they do experience catch up growth, particularly if they have been exposed to the adverse effects on lung growth of postnatally administered corticosteroids [22].

BPD has also been determined to be an independent risk factor for long-term neurodevelopmental adverse outcomes. In infants whose birth weights were 500 to 1000 g, the presence of BPD (defined at 36 wk) was associated, independent of other risk factors, with a doubling in the incidence of neurodevelopmental morbidity at 18 months corrected age [24]. Associations have been identified between poor developmental outcome and prolonged hospitalisation or prolonged ventilation. The neurodevelopment of BPD children could be damaged by the use of systemic steroids [25].

Thus, BPD represents a serious health problem associated with mortality and high morbidity among graduates of the neonatal intensive care units. The cost of BPD is tremendous. It is associated with prolonged hospitalization of the preterm infant, multiple rehospitalisations during the first few years of life, and survival with developmental delay and/or cerebral palsy. That is why expansion of our insights into pathogenesis and epidemiology of BPD is important for the elaboration of its effective prevention and treatment strategies.

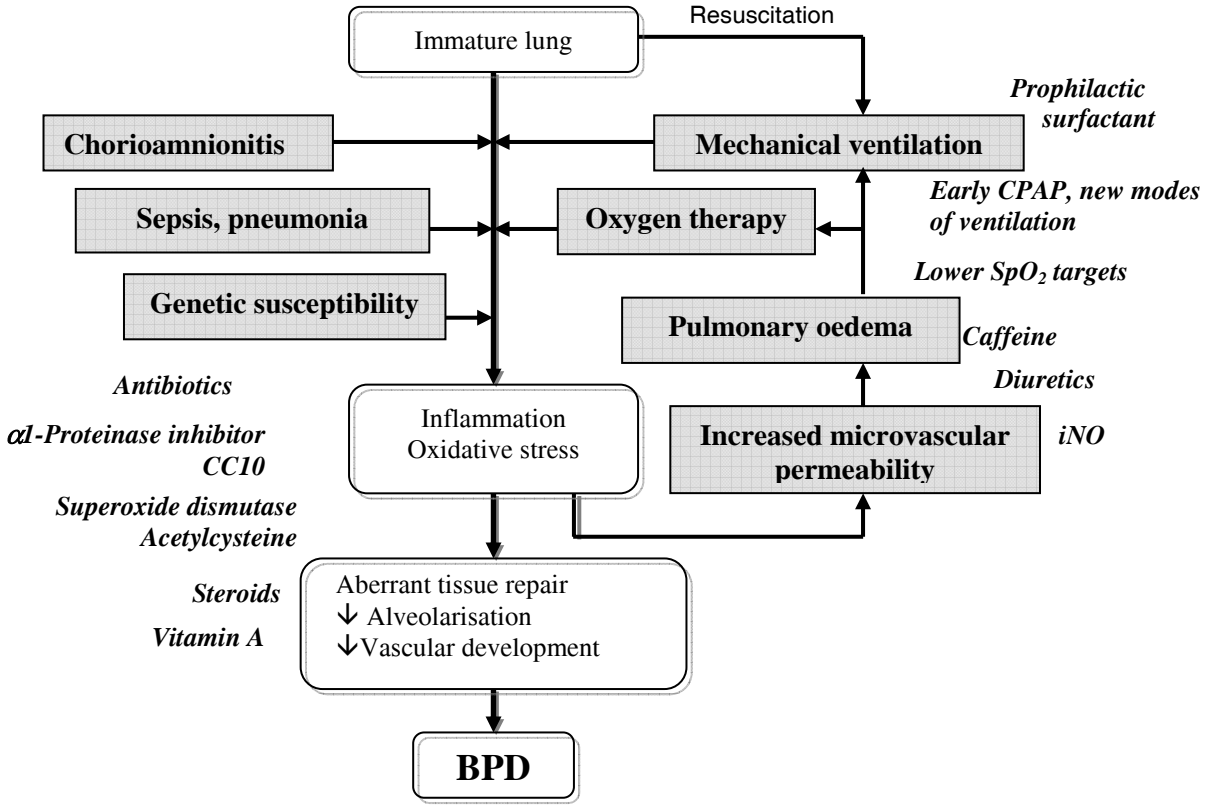

FIGURE 2. Simplified pathogenetic sequence leading to BPD and potential interventions (iNO – inhaled nitric oxide; CC10 – Clara Cell 10 kDa protein); adapted from Thomas and Speer [27]

PATHOGENESIS

BPD has a multifactorial aetiology which refers to foetal infection or inflammation, antenatal steroids, oxidant stress, ventilator induced lung injury, postnatal inflammation/infection, inadequate nutrition, genetic factors, and abnormal growth-factor signalling [25]. Briefly, a shifted to the inflammatory side balance in the release of pro- and anti-inflammatory cytokines as well as proteinase-antiproteinase imbalance, occurring as a result of influence of the risk factors shown in Fig. 2, damages immature lung. This is followed either by healing (resolution of injury) or aberrant repair of the lung with impaired alveolarisation and vascular development (BPD). Cytokine release and the responses of the immature lung are determined by allelic differences of the genes, creating a genetic susceptibility to BPD [26].

PREVENTION AND TREATMENT

Many strategies to prevent or ameliorate BPD have been evaluated so far (Table 1, Figure 2).

The strongest evidence for a long-term preventive effect exists for the repetitive intramuscular administration of high doses of vitamin A. Its supplementation with an intramuscular dose of 5000 IU three times a week for the first 28 days of life conferred a modest reduction (about 7%) in rates of supplemental oxygen administration at 36 weeks' corrected gestational age [28]. At the same time because of practical limitation of intramuscular medication use in very low birth infants in many centres this kind of therapy is not routinely used [27]. In a recent large cluster-randomized benchmarking study use of vitamin A, early administration of surfactant, and maintaining lower oxygen saturation in the newborns most of whom were intubated and ventilated in the delivery room have not lowered the incidence of BPD in the 4095 recruited infants [29].

Despite the clear cause-and-effect relationship between the ventilation and lung injury, most of the studies have not been designed to avoid intubation and instead have been conducted to test every possible strategy for reducing lung injury in already-intubated and –ventilated infants. Two decades of observational studies have failed to resolve the debate regarding the merits of CPAP with respect to BPD prevention, but with frustration of not having a "magic bullet" to prevent or control BPD, an increasing number of NICUs are reporting their experience of less BPD when using early CPAP and other methods of non-invasive ventilation shortly after birth [30].

New ventilation techniques introduced in an effort to improve neonatal outcomes include synchronized and assist-control modes, volume-targeted ventilation as well as different types of high frequency ventilation (HFV). None has yet consistently proven efficacy in reducing death or BPD. The overall meta-analyses showed no benefit of HFV in the composite outcome of death or BPD (RR 0,87; 95% CI 0,75-1,00) [31, 32], however, revealed important benefits of volume-targeted ventilation with respect to secondary morbidities [33].

The effects of iNO in the premature newborn may be dependent on the timing, dose, and duration of therapy, and on the nature of the underlying disease. The available evidence from clinical trials suggests that low-dose iNO may be safe and effective in reducing the risk of death/BPD for a subset of premature newborns, in particular infants with birth weights >1000 g [34]. But currently, there is still insufficient evidence for a routine use of iNO for the prevention of the disease.

Oxygen supplementation remains an important therapeutic strategy for patients with established BPD. The most appropriate range of arterial oxygenation in preterm infants with acute or chronic respiratory failure is not known. However, high levels of oxygen saturation appear to offer no advantages, and pulmonary injury may result from the increased concentration of supplemental oxygen required to maintain higher saturations, as shown by two recent studies [35, 36]. Targeting the infants at lower oxygen saturation seems to reduce long-term pulmonary morbidity without significantly increasing the risk of adverse neurosensory outcome.

Despite the fact that according to the conclusions of meta-analysis of the all eligible studies neither prophylactic no rescue treatment with natural surfactants reliably prevents BPD, at least for one surfactant preparation it was shown that prophylactic or very early treatment administration in very immature infants may have a beneficial effect on the incidence of BPD [37]. Late administration of surfactant might also ameliorate respiratory signs and reduce the barotrauma, oxygen toxicity and inflammation associated with periods of respiratory deterioration in preterm infants with evolving BPD.

TABLE 2. Strategies to prevent or ameliorate BPD and existing evidence

Proven benefit for BPD	Short-term benefits on lung function, no proven effect on BPD	Controversial data, no definite conclusion	No proven benefit
Vitamin A supplementation Systemic post-natal corticosteroids[a] Caffeine[b] Prophylactic surfactant Targeting lower SpO_2	Diuretics Inhaled nitric oxide Bronchodilators	Low-dose hydrocortisone Early CPAP High frequency ventilation Inhaled nitric oxide Permissive hypercapnia	Superoxide dismutase, N-acetylcysteine α1-Proteinase inhibitor Erythromycin Intensive nutritional supplementation Thyroxin supplementation Inhaled corticosteroids

[a] No routine therapy because of severe short- and long-term side effects.
[b] Definite assessment of long-term neurosensory outcome is pending, routine use can currently not be recommended.

Administration of systemic corticosteroids can reduce the risk for BPD at either 28 days of life or 36 wks corrected gestational age but without affecting mortality [38, 39, 40]. However, in face of the potential short- and long-term adverse effects – especially with those of early administration on the increased risk of cerebral palsy – they should be restricted to the severest cases of BPD with a high risk of death from respiratory failure. Currently, there is no evidence that early inhaled corticosteroids confer important advantages over systemic steroids in the prevention of BPD [41].

Watterberg and co-workers were the first to show that early low-dose hydrocortisone treatment was associated with a reduction in BPD among the treated infants [42]. These findings are also consistent with information from a recent trial which confirmed the same effect [43]. Several other studies in which infants were treated with early low-dose hydrocortisone showed no evidence of neurodevelopmental compromise at 18 to 22 months adjusted age or later in childhood compared with infants who were treated with placebo [44, 45]. These data provide an encouraging foundation for pursuing future studies of hydrocortisone therapy for BPD.

A temporary use of diuretics can improve lung function and oxygenation. Nonetheless, existing data do not justify a sustained diuretic therapy. Infants with BPD treated with beta-agonists or other bronchodilators may respond with a short-term increase in compliance and tidal volume, and decrease in airway resistance. However, this treatment has not been shown to affect long-term outcome.

Meta-analyses of observational studies favour a role of *U. urealyticum* in the pathogenesis of BPD. However, interpretation of results from trials of erythromycin and azithromycin in the prevention of the disease is hampered by small sample sizes.

Rigorously conducted studies of α1-proteinase inhibitor, using two different treatment regimens, failed to show their benefit as regards mortality or oxygen requirement at 36 weeks' corrected age, independently or in a meta-analysis of all 195 infants involved [46]. Human studies of clinical effectiveness of superoxide dismutase and N-acetylcysteine failed to show a benefit in BPD prevention [47, 48].

The early administration of caffeine for prophylaxis and treatment of apnoea of prematurity has most recently been shown to reduce the risk of BPD [49]. However, the definite assessment of the primary outcome of the caffeine trial is needed before its routine use can be recommended for the prevention of BPD.

Future preventive therapies for BPD are likely to include targeted cytokine or anti-cytokine therapies aimed at upregulating beneficial and blocking harmful humoral factors. An example of one such therapy is antimacrophage chemokine (anti-MCP-1). Other candidates for future therapies include: anti-inflammatory agents (e.g. interleukin-10), surfactant proteins, Clara cell secretory protein and bombesin-blocking molecules.

MONITORING

Infants with CLD need close monitoring to minimise further lung injury, reduce the risks of pulmonary and systemic hypertension, and promote adequate growth and development. This should begin during hospitalisation and continue after discharge.

The major approach to avoid or treat pulmonary hypertension is maintaining adequate oxygenation, although pharmacologic treatment may

be required in severe cases. In general, in infants with severe CLD who do not have pulmonary hypertension, oxygen saturations (SaO_2) are maintained 88–94%; in those infants with pulmonary hypertension, saturations are maintained somewhat higher (94–96%) [50]. Serial echocardiography is performed every 2–3 months in infants who require prolonged mechanical ventilation and supplemental oxygen or who have developed pulmonary hypertension. Patients with pulmonary hypertension should be followed by a paediatric cardiologist.

Hospitalised infants should be weighed two to three times per week, and length and head circumference should be measured weekly. Biochemical monitoring including measurement of blood urea nitrogen, albumin, calcium, phosphorus, and alkaline phosphatase, may assist with nutritional assessment. Serum electrolytes should be followed in infants on diuretic therapy, and supplements provided as needed.

Developmental assessment should begin while the infant is still hospitalised and continue on a regular basis after discharge. Infants should have serial eye examinations to detect retinopathy of prematurity or other eye disorders, and receive appropriate intervention. Routine hearing screening should be performed to detect impairment, with early intervention by an audiologist if needed.

DISCHARGE PLANNING

Infants with severe CLD usually have a prolonged hospitalisation, and require substantial planning for discharge to home and post-discharge care. Discharge should be planned by a multidisciplinary care team. The basic requirements for home discharge include stable SaO_2 for at least 2 weeks, parents willing and felt to be able to cope with home oxygen and other needs of baby, no apnoeas for at least 2 weeks, no change in medications for the last week, parents have telephone, infant either fully orally fed, or tube fed (if tube fed, parents can pass tubes and feed baby competently), parents have been taught resuscitation, especially if apnoea monitor provided, and community support staff are available in the following 2–3 days (i.e. not just before a weekend or holiday) [51].

CONCLUSIONS

Bronchopulmonary dysplasia is a chronic lung disease which is characterised by multifactorial aetiology and association with preterm birth. Significant changes in its definition, pathology, pathophysiology, clinical course, radiological findings and management have occurred over the last 40 years. BPD has evolved to be characterised largely by inhibition of lung development. Substantial progress has been made in understanding optimal management of infants with evolving and established BPD. Current interventions, while providing acute benefit, have not been shown to improve long-term outcomes. Additional researches are needed to fully understand the pathogenesis of BPD and develop improved interventions in the prevention and management of the condition.

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