LONG TERM RESPIRATORY SEQUELAE OF PREMATURE BIRTH

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Abstract

Long term respiratory sequelae of premature birth are common. No safe and preventative strategy has been identified.

Introduction

Long term respiratory sequelae of premature birth are very common and include chronic oxygen dependency, troublesome respiratory symptoms during childhood and lung function abnormalities seen even in adolescents and young adults (Table 1). Such problems are more likely if the infants have been oxygen dependent at least for a month after birth. The incidence of chronic oxygen dependency is increasing, primarily due to the improved survival of very prematurely born infants. The long respiratory sequelae of premature birth are, therefore, extremely important, both with regard to counselling parents and planning health service allocation.

Table 1. *Long term respiratory sequelae*

- A high readmission rate, particularly in preterm infants who developed BPD and/or had an RSV infection
- Chronic oxygen dependency requiring supplementary oxygen at home
- Troublesome respiratory symptoms at school age requiring "anti-asthma" medication.
- Lung function abnormalities in adolescence associated with poor exercise tolerance.

Diagnosis

Infants who were chronically oxygen dependent following premature birth were previously described as suffering from chronic lung disease. The term bronchopulmonary dysplasia (BPD) is now preferred as it is more specifically associated with infants. BPD was first reported by Northway in 1967 and described infants who were chronically oxygen dependent and developed distinctive chest radiograph appearance abnormalities. Severe cystic lesions characterising stage four BPD (Figure 1) such chest radiograph changes are now relatively uncommon.

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As a consequence, following recommendations made at a National Institute of Health (NIH) Workshop.[1] BPD has been used as an umbrella term to describe any chronically oxygen dependent infant regardless of their chest radiograph appearance (new BPD) (Figure 2). Infants are diagnosed as having BPD if they are oxygen dependent beyond 28 days after birth. Such infants are subsequently classified as suffering from mild, moderate or severe BPD depending on their supplementary oxygen and respiratory support requirements closer to term.

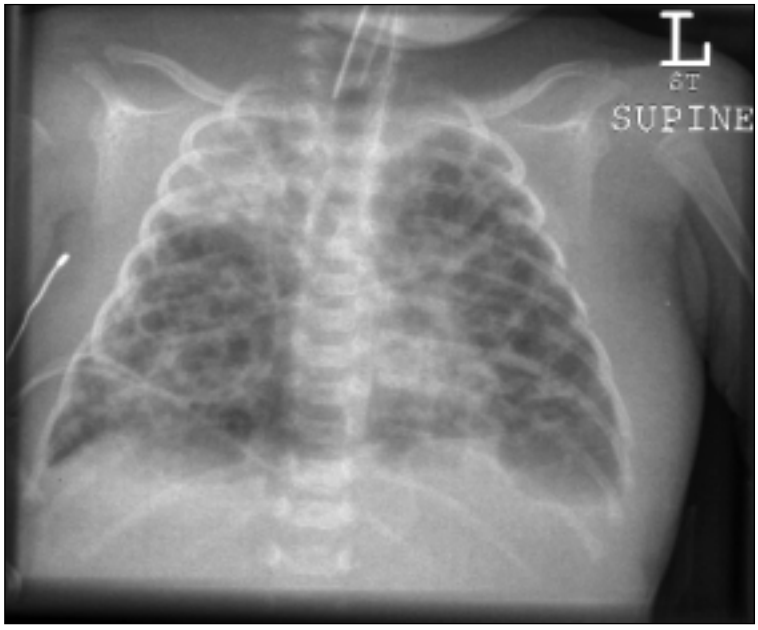

Figure 1. *Chest radiograph of an infant with "old BPD – Northway stage 4, note the cystic lesions which are particularly marked at the lung bases.*

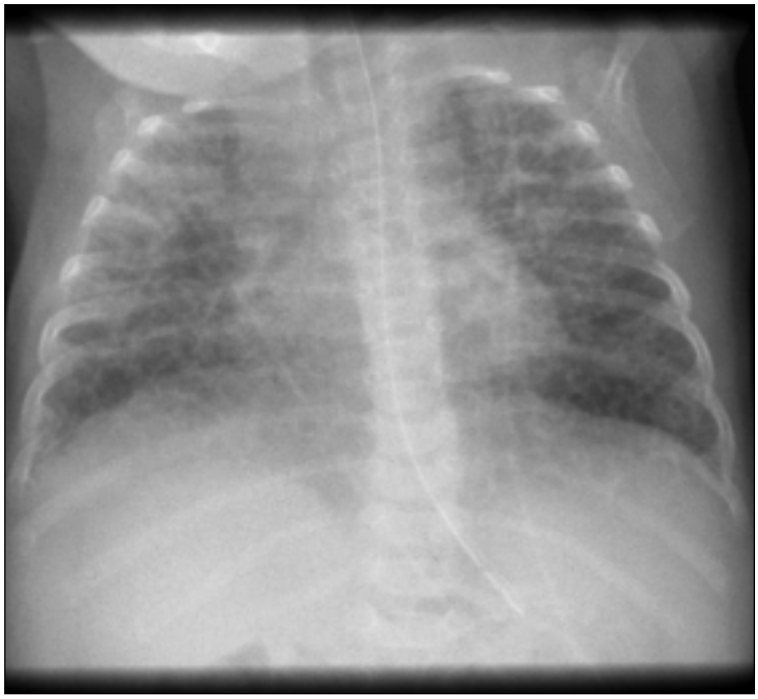

Figure 2. *Chest radiograph of an infant with "new" BPD – note the hazy lung fields and low lung volumes.*

Table 2. *Risk factors for bronchopulmonary dysplasia*

- Very premature birth
- Low birthweight
- Surfactant deficiency (respiratory distress syndrome)
- Oxygen toxicity
- Volutrauma
- Fluid overload/patent ductus arteriosus
- Antenatal or nosocomial infection
- Family history (of atopy)

The aetiology of BPD is multifactorial, premature birth and low birthweight being amongst a number of risk factors. Antenatal risk factors include chorioamnionitis; as antenatal infection may adversely affect lung development. Postnatal risk factors include volutrauma (lung overdistension) and oxygen toxicity have been incriminated, although increasingly it is recognised that BPD may develop in a premature infant with minimal or no respiratory disease immediately after birth. Fluid overload and the development of a patent ductus arteriosus (PDA), particularly if there is also nosocomial infection, are also important risk factors. In some infants, there is a family history of BPD, but whether a family history of atopy is important remains controversial.

Long term sequelae

(i) Chronic oxygen dependency

Premature infants may require supplementary oxygen at home for many months, even years and it is important to counsel parents accordingly.[2] Infants have usually been considered for home oxygen therapy if they have had no other ongoing medical need. Inclusion of infants who additionally require tube feeding has been shown to allow infants to be discharged home two weeks earlier, with no excess morbidity and an overall reduction in the cost of care.[3] Prior to discharging an infant home in oxygen it is essential a multidisciplinary meeting is held to ensure there is adequate community support, the home circumstances are suitable and that the parents are familiar with the equipment and capable of basic life support. Results of recent trials suggest that for the majority of premature infants, the target oxygen saturation level during home oxygen therapy should be between 91 and 94%.[4] It is likely that infants with pulmonary hypertension would benefit from higher oxygen saturation levels, but this has not been investigated in randomised trials with long term outcomes.

(ii) Rehospitalisation

Rehospitalisation is required in up to 50 percent of "BPD" infants in the first year and between 20 and 30% in the second year. Infants with BPD may be readmitted five times on average during the first two years after birth; rehospitalisation is much more common in those infants who require supplementary oxygen at home.[5] The primary reason for hospitalisation is lower respiratory tract infections, particularly due to RSV.[6] The rehospitalisation rate is approximately doubled if a premature infant requires supplementary oxygen at home or has had an RSV infection.

(iii) Respiratory symptoms

Prospective follow up of prematurely born infants has demonstrated that at least 50 percent are symptomatic in the first year and 35 percent in the preschool years. The occurrence of troublesome respiratory symptoms is much higher in infants who remained oxygen dependent beyond 36 weeks postmenstrual age. Even at school age, prematurely born children are more likely to have respiratory symptoms than their classroom colleagues born at term. In one study, every additional week of gestation reduced the likelihood of wheeze by ten percent.

(iv) Lung function abnormalities

Prematurely born infants (particularly those who developed BPD) have evidence of airways obstruction (high airways resistance and gas trapping) in the first two years after birth. Those lung function abnormalities frequently improve in response to bronchodilator administration.[7] As the children's clinical condition improves,

so does their lung function, but lung function abnormalities can still be demonstrated at school age. Affected children have airways obstruction and exercise intolerance. Adolescents who had BPD, although asymptomatic at rest, may desaturate on exercise testing. Those studies, however, report the outcome of children born more than ten years ago, who were not routinely exposed to antenatal steroids or postnatal surfactant and thus often had a severe initial respiratory illness.

Nowadays, infants who are chronically oxygen dependent are described as suffering form "new BPD" and many have had minimal or no respiratory illness. The few pathological reports of this condition highlight that affected infants have minimal small airway injury and less prominent inflammation and fibrosis, but decreased alveolarisation. As a consequence, it has been proposed that new BPD is not the injury repair paradigm of traditional BPD, but a maldevelopment sequence resulting from interference/interruption of normal development signalling for terminal maturation and alveolarisation of the lungs of very premature infants.[1] Results from preclinical models have also demonstrated decreased alveolariastion and a decreased total internal lung surface area.[8] Our preliminary evidence has highlighted infants with new "BPD" have small lungs at follow up. Affected infants, then, are likely to be at high risk of chronic respiratory morbidity. Longitudinal studies are required to monitor the outcome of such vulnerable patients.

Preventative strategies

Neither administration of antenatal steroids nor postnatal surfactant, although reducing the development of respiratory distress syndrome, decrease the incidence of BPD; the likely explanation being that both antenatal steroids and postnatal surfactant significantly reduce mortality and hence more vulnerable preterm infants at risk of BPD survive. Both oxygen toxicity and volutrauma have been implicated in the causation of BPD, this has stimulated research to identify the mode of ventilation associated with the lowest BPD rate. Numerous randomised controlled trials have been carried out, but, overall, neither patent triggered ventilation[9] nor high frequency oscillation[10,11] have been demonstrated to reduce the incidence of BPD. Fluid overload increases the risk of PDA and hence BPD, and although fluid overload should be avoided, randomised trials of fluid restriction have not shown this strategy to reduce BPD.[12] Inhaled nitric oxide, a selective pulmonary vasodilator, can improve oxygenation in prematurely born infants with severe respiratory failure, but in that group does not reduce BPD. Inhaled nitric oxide may, however, promote angiogenesis and hence alveolarisation; as a consequence whether prophylactic inhaled nitric oxide given soon after birth, may reduce BPD development is currently being investigated. The only effective proven method of preventing BPD is to systemically administer corticosteroids in the first two weeks after birth. Unfortunately, follow up studies have shown such a strategy is associated with an increased risk of adverse neurodevelopment outcome at follow up.[13] To date, than no safe and effective strategies to prevent BPD have been identified.

Table 3. *Management of the respiratory sequelae*

- Supplementary oxygen at home to maintain appropriate oxygen saturation levels
- Bronchodilator therapy for children wheezy at follow up
- Prophylactic anti-asthma medication eg. Inhaled corticosteroids for those with frequent troublesome wheeze
- Prevention of RSV infection
  - education of parents and staff about hand-washing and reducing the risk of exposure to RSV
  - passive immunoprophylaxis to high risk cases eg those receiving supplementary oxygen at home

To prevent further lung damage in premature infants who remain chronically dependent on respiratory support, the ventilator pressures and inspired oxygen concentrations should be reduced to the minimum compatible with acceptable blood gases and every effort made to wean infants from the ventilator. Infants with BPD are often intolerant of standard maintenance volumes of fluid/feeds. In such infants, diuretics may be useful, and can acutely improve lung function, but randomised trials have demonstrated that their administration does not result in any long term benefits. BPD infants have prebronchial smooth muscle hypertrophy and can have a positive response to bronchodilator administration while on the neonatal unit, but such effects are short-lived. After

discharge, therapy with inhaled anticholinergic or _ agonist bronchodilators, utilising a coffee cup spacer device, has been shown to improve lung function and reduce symptoms, in wheezy low birth weight infants.[14,15] Prophylactic ant-asthma medication, inhaled sodium cromoglycate or corticosteroids, reduces bronchodilator requirement and improves lung function again in wheezy preterm infants seen at follow up.[16,17]

RSV infection increased respiratory morbidity at follow up in prematurely born infants who developed BPD.[6] There is no safe and effective vaccine against RSV, but immunoprophylaxis has been shown to reduce the hospitalisation rates for RSV infection of prematurely born infants, with or without BPD. This positive effect has been demonstrated both for RSV immunoglobulin (RSV-IGIV)[18] which contains high levels of RSV neutralising antibodies and Palivizumab,[19] a humanised monoclonal antibody. Palivizumab, however, is the preferred prophylactic agent as it is given intramuscularly rather than intravenously so does not need to be given in the hospital setting, and it may be more effective and is safer. Problems were encountered with RSV-IGIV perhaps because of the volume given intravenously and hyperviscosity. Nevertheless, it has been suggested that administration of Palivizumab may not be cost effective, except in preterm infants who are oxygen dependent in the community. Those studies, however, only took into account the potential savings related to the initial hospitalisation episode and a different picture may emerge if the chronic respiratory morbidity following RSV infection is taken into account.

Summary

The long term sequelae of premature birth are common and include chronic oxygen dependency, troublesome wheeze and cough and lung function abnormalities, with impaired exercise tolerance even in adolescence. The most vulnerable infants are those born very prematurely, particularly if they subsequently develop bronchopulmonary dysplasia and subsequently suffer an RSV infection A safe and effective preventative strategy is urgently required.

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