CURRENT TOPIC

Bronchopulmonary dysplasia: then and now

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Bronchopulmonary dysplasia was first described in 1967 in a series of 32 infants with severe respiratory distress syndrome who were treated with artificial ventilation and supplemental oxygen.¹ These infants had initially been given antibiotics, the usual measures for control of body temperature, and glucose and sodium bicarbonate intravenously to combat acidosis. They had not responded to this treatment, were cyanotic in 100% oxygen, looked moribund, and had had one or more prolonged apnoeic spells. The clinical and radiological progression of respiratory distress syndrome was significantly modified by treatment with prolonged positive pressure ventilation, and 80-100% concentrations of oxygen. What was remarkable was the appearance of a new syndrome of chronic lung disease that was called bronchopulmonary dysplasia. The usual course of respiratory distress syndrome before the use of prolonged positive pressure ventilation was that infants who survived the first 3 days of life recovered completely and by 7-10 days of life had normal lungs radiographically.² Those who died did so within four days. Chronic lung disease had not been seen as a sequel to respiratory distress syndrome before the description of bronchopulmonary dysplasia.

The clinical, radiological, and pathological progression of bronchopulmonary dysplasia was initially divided into four stages.¹ Stage I (days 1-3) consisted of the initial clinical and radiological picture of respiratory distress syndrome. During stage II (days 4-10) there was increasing opacification of the lungs and, if the infant died, there was thick exudation into the lumen of the airway with patchy bronchiolar and alveolar epithelial necrosis with early stages of repair. At the end of stage II, weaning of the infants from the high concentrations of oxygen (80-100%) could usually be started. Stage III (days 10-20) was a period of transition to chronic lung disease with the chest radiograph showing a reticular network of small rounded areas of radiolucency that represented areas of emphysematous alveoli adjacent to atelectatic alveoli, and pulmonary fibrosis. This stage could be complicated by patent ductus arteriosus and congestive heart failure. In stage IV (after 30 days of age) there was persistent chronic lung disease with hyperexpansion and cystic looking lungs. The electrocardiogram at this stage usually showed right ventricular hypertrophy and cardiomegaly with cor pulmonale. Pathologically, there was emphysema with thickening

of the lung interstitium, replacement of type I pulmonary epithelial cells with type II pneumocytes, squamous metaplasia and ulceration of bronchiolar epithelium, hypertrophy of bronchiolar smooth muscle, and early vascular lesions indicating pulmonary hypertension with periarteriolar thickening.

Since the original description of bronchopulmonary dysplasia, it has been described all over the world in places where artificial ventilation and supplemental oxygen have been used to treat infants with severe respiratory distress syndrome. Bronchopulmonary dysplasia has become the most common form of chronic lung disease in infancy in the United States, with about 7000 new cases occurring each year (35 000 cases of respiratory distress syndrome/year times a 0.20 incidence of bronchopulmonary dysplasia/per case of respiratory distress syndrome).³

Pathogenesis

The principal factors in the the pathogenesis of bronchopulmonary dysplasia are (i) premature birth, (ii) respiratory failure, (iii) oxygen toxicity, and (iv) barotrauma. Premature birth is associated with immature lung structure, lack of surfactant, and inadequate respiratory drive, all of which contribute to respiratory failure. Respiratory failure is critical in the pathogenesis because it requires treatment with supplemental oxygen and artificial ventilation. The respiratory failure may be from any cause, but is most commonly from respiratory distress syndrome. The interaction of the concentration and duration of supplemental oxygen and the immaturity of the lung determines in part the development of bronchopulmonary dysplasia.⁴ Since 1967 the supplemental oxygen concentration used in treating respiratory distress syndrome has been reduced, and many of the infants are less mature. The premature infant who requires supplemental oxygen is at risk of oxygen injury to the lung because the immature antioxidant activity, both enzymatic and non-enzymatic, may not be sufficient to protect against the increased generation of oxygen radicals.⁵ The effects of prolonged exposure to concentrations of supplemental oxygen of less than 60% on the immature human or animal lung are not known. Positive pressure ventilation is important in the pathogenesis of bronchopulmonary dysplasia because it facilitates the delivery of supplemental oxygen and can further injure the lung by

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barotrauma. Pulmonary interstitial emphysema and pneumothorax are the most obvious clinical findings of barotrauma, but damage to the small airways in the surfactant deficient lung can occur without actual rupture of the wall of the airway.⁶ Factors that prolong artificial ventilation and supplemental oxygen therapy contribute to the degree of severity of bronchopulmonary dysplasia and include pulmonary air leak (interstitial emphysema, pneumomediastinum, and pneumothorax), pulmonary oedema (patent ductus arteriosus, cor pulmonale, congestive heart failure, and fluid overload), and pulmonary infection. *Ureoplasma urealyticum* has recently been isolated more often from prematurely born infants who developed bronchopulmonary dysplasia than those who did not, but respiratory distress at birth was not associated with colonisation with the organism.⁷ The part played by *U urealyticum* in the pathogenesis of bronchopulmonary dysplasia remains to be determined.

Pathology

The changes in the bronchiolar regions in bronchopulmonary dysplasia have been attributed both to barotrauma and to pulmonary oxygen toxicity. Overdistension of airways and irregular aeration of the alveoli can produce sheer forces in the airway mucosa that lead to disruption of the epithelium during artificial ventilation.⁸ Necrotising bronchiolitis and squamous metaplasia similar to those seen in bronchopulmonary dysplasia are seen with experimental pulmonary toxicity in newborn mice.⁹ The inflammatory cells that accumulate about the small airways and in the alveolar walls amplify the structural damage and enhance the recruitment and proliferation of fibroblasts, which leads to accumulation of type I collagen in these areas.¹⁰ Derangement of pulmonary tissue with almost complete loss of the lung's normal architecture associated with extensive interstitial and interalveolar fibrosis has consistently been described in pathological studies of bronchopulmonary dysplasia.¹¹⁻¹³ Increased numbers of pulmonary inflammatory cells have been well documented in serial bronchoalveolar lavage fluid samples from newborn infants with respiratory distress syndrome who subsequently developed bronchopulmonary dysplasia.^{14 15}

Associated with the large numbers of neutrophils in these infants are sustained high elastase, and low α_1 -protease inhibitor, activities. This elastase-protease inhibitor imbalance promotes hydrolysis of the connective tissue matrix. As the inflammatory process progresses, alveolar macrophages become more prominent in bronchoalveolar lavage fluid. They also produce

an elastase and, when injured, can accelerate the release of neutrophil elastase.¹⁶ Proteolytic enzymes released by inflammatory cells may play an important part in the damage of epithelial and connective tissue in bronchopulmonary dysplasia. Preterm infants may be more susceptible to injury by the proteolytic enzymes because they have low concentrations of serum proteins, including the antiproteases.¹⁷ Because these proteolytic enzymes and the byproducts of the injuries that they cause appear in bronchoalveolar lavage fluid before there is clinical and radiological evidence of bronchopulmonary dysplasia, they may prove useful as early indicators of development of the disease.

Animal experiments

A prematurely delivered immature baboon model for bronchopulmonary dysplasia has been developed.¹⁸ The prematurely delivered baboon develops a syndrome similar to respiratory distress syndrome, and requires artificial ventilation with supplemental oxygen to survive. Treatment with prolonged artificial ventilation and oxygen supplementation does result in the production of stage III bronchopulmonary dysplasia in the immature baboon. It has not been possible with this animal model, however, subsequently to eliminate any of the contributing factors to test the hypothesis that any one of them alone can produce a continuum of pathology similar to bronchopulmonary dysplasia. To date the only single factor that has been shown to produce a continuum of pathology similar to bronchopulmonary dysplasia in its acute, subacute, and chronic forms in a newborn mammalian lung is pulmonary oxygen toxicity.¹⁹

Incidence

A comparison of the incidence of bronchopulmonary dysplasia in infants with severe respiratory distress syndrome at the Stanford University Medical Center from the original report (1962-1965) and from 1989 is presented in the table. Compared with 1962-5, there was a pronounced decrease in bronchopulmonary dysplasia in 1989 among infants who weighed more than 1500 g at birth ($p<0.05$). The overall incidence of bronchopulmonary dysplasia in infants with severe respiratory distress syndrome, however, was not significantly decreased in 1989 compared with 1962-5 because of an increased incidence in infants with respiratory distress syndrome who weighed less than 1500 g. Of note is the high incidence of bronchopulmonary dysplasia among premature

No (%) with stage IV bronchopulmonary dysplasia (BPD) among infants with respiratory distress syndrome (RDS) treated with positive pressure ventilation and oxygen for more than 24 hours

	1962-5: birth weight (g)				1989: birth weight (g)			
	<1000	1000-1500	>1500	Total	<1000	1000-1500	>1500	Total
BPD/RDS (%):								
Survivors	0/0 (0)	1/2 (50)	3/11 (27)	4/13 (31)	22/30 (73)	8/34 (24)	3/47 (6)	33/111 (30)
Non-survivors	0/3 (0)	2/5 (40)	3/11 (27)	5/19 (26)	3/5 (60)	0/2	1/1 (100)	4/8 (50)
Total	0/3 (0)	3/7 (43)	6/22 (27)	9/32 (28)	25/35 (71)	8/36 (22)	4/48 (8)	37/119 (31)

This table is a shortened and updated version of that published in *Respiratory Distress Syndrome* (Kari O Raivio, Niilo Hallman, Kauko Kouvalainen, Ilkka Välimäki, eds) by Academic Press, 1984.

infants with respiratory distress syndrome weighing less than 1000 g in 1989. In 1962–5, infants weighing less than 1000 g were not artificially ventilated, as the techniques were not sufficiently developed to apply them to these very low birthweight (VLBW) infants. The high incidence of bronchopulmonary dysplasia in VLBW premature infants is an increasing problem.

Radiological changes

The progression of radiological change has been modified as stage IV bronchopulmonary dysplasia has become more common in infants weighing 1000 g or less, and as supplemental oxygen concentrations and peak inspiratory pressures and their durations have decreased.²⁰ The initial radiograph is usually of immature lung or respiratory distress syndrome, but the lungs may not become completely opaque within the first few days of treatment as originally described, but instead remain persistently hazy for several weeks. At 3 or 4 weeks of age the hazy opacification changes into a fine reticular pattern, with or without hyperexpansion. This reticular pattern may first be noted at 30 days of age, but can initially be seen even later. Its initial appearance may be masked by pulmonary oedema, pneumonia, or poor inspiration. The characteristic radiographic progression of bronchopulmonary dysplasia that was originally described still occurs in the more severely ill infants, particularly those whose course is complicated and prolonged by infection, congestive heart failure, fluid overload, or interstitial emphysema.

The incidence of bronchopulmonary dysplasia seems to be considerably higher in infants who develop pulmonary interstitial emphysema.²¹ If the interstitial emphysema is diffuse and persistent, the characteristic radiographic appearance of chronic bronchopulmonary dysplasia will be difficult to differentiate from pulmonary interstitial emphysema. If pulmonary interstitial emphysema persists until the infant is 3 weeks of age, the patient invariably also has bronchopulmonary dysplasia.

Diagnosis

As bronchopulmonary dysplasia has evolved and the radiographic picture has been modified, the diagnostic criteria have become more clinical and physiologically oriented. The diagnosis of bronchopulmonary dysplasia (usually meaning stage IV or chronic disease) includes assessment at 3 or 4 weeks of age, a history of artificial ventilation and supplemental oxygen for at least 24 hours, signs of respiratory distress including an abnormal respiratory rate (greater than 40/minute), persistent intercostal retractions, raised carbon dioxide tension (or requirement for supplemental oxygen for longer than 3 or 4 weeks), and persistent abnormalities on chest radiographs. This approach to the diagnosis of bronchopulmonary dysplasia (recommended by Farrell and Palta) relies on signs and symptoms of the infant's respiratory disease rather than on therapeutic decisions by the physician and

should be more replicable among neonatal intensive care nurseries.³

Outcome

Increased airway resistance, increased airway reactivity, low dynamic compliance, increased functional residual capacity, increased respiratory rate, high arterial carbon dioxide tension, low arterial oxygen tension, severe maldistribution of ventilation, right or left (or both) ventricular hypertrophy, pulmonary hypertension, and systemic hypertension have been shown in surviving 1 to 2 year old infants with bronchopulmonary dysplasia.^{22–31} These abnormalities of cardiopulmonary function can improve with age but may not resolve.²⁵ Airway obstruction, airway hyper-reactivity, abnormal arterial capillary blood gas values, radiological abnormalities, increased lung volume, and electrocardiographic abnormalities have been found in nine children with a history of bronchopulmonary dysplasia at an average age of 8.4 years.³² Increased lung volumes, airway obstruction, and increased transcutaneous carbon dioxide tension have been documented in a group of 10 children with an average age of 10.4 years who had bronchopulmonary dysplasia.³³ We have recently shown that most of 22 young adults age 14–23 years who had had bronchopulmonary dysplasia, had pulmonary dysfunction consisting of airway obstruction, airway hyper-reactivity, and air trapping when compared with 20 ex-prematurely born young adults of the same age and 48 normal volunteers of the same age.³⁴

Injury to small airways in premature infants' lungs has been a prominent feature and a particularly disturbing aspect of the pathology of bronchopulmonary dysplasia.⁹ The possible relationship between lower respiratory illness in childhood and chronic airflow obstruction in adulthood was reviewed by Samet *et al.*³⁵ Injury to the small airways was the common feature of the respiratory illnesses in childhood, such as infection with respiratory syncytial virus, which might be associated with chronic airway obstruction. In a series of 40 prematurely born infants who had survived artificial ventilation for respiratory insufficiency, 70% had one or more episodes of pneumonia or bronchitis during the first 2 years of life.³⁶ There was a direct relationship between the presence of bronchopulmonary dysplasia and the number of lower respiratory tract infection. A four month prospective study of 30 children less than 2 years old with bronchopulmonary dysplasia showed that 59% developed respiratory syncytial virus infection and 70% of those required admission to hospital.³⁷ Premature infants who develop bronchopulmonary dysplasia may be predisposed to have an increased incidence of lower respiratory illnesses and to develop obstructive airways disease as adults.

Many infants with bronchopulmonary dysplasia are below the third centile for height and weight during the first 2 years of life,³⁸ and persistent growth delay may persist throughout early childhood and beyond. Our follow up study of young adults who had had broncho-

pulmonary dysplasia indicated that, as a group, they were slightly but significantly shorter and lighter than the normal or prematurely born age matched control group.³⁴

Neurodevelopmental deficits have also been reported to occur more often in infants and children with bronchopulmonary dysplasia. It is not clear whether these are caused by bronchopulmonary dysplasia or by some perinatal or neonatal event.³⁸⁻³⁹ Neurological abnormalities have been reported in 0 to 38% of premature infants with a diagnosis of bronchopulmonary dysplasia.⁴⁰ Developmental abnormalities measured by the Bayley Scales Mental Development Index ranged from 14% to 80% in infants with bronchopulmonary dysplasia. Only one study looked at children as old as 8 years of age, and no significant effect of bronchopulmonary dysplasia on neurodevelopmental outcome was found.⁴¹ Late evaluation of growth and development in young adults who had had bronchopulmonary dysplasia deserves further attention.

Treatment

Reducing the incidence of premature births would be the single most effective way of reducing the incidence of bronchopulmonary dysplasia, and this is both a scientific and a socioeconomic problem. Medical complications of pregnancy and fetal factors leading to premature delivery can be reduced, but not eliminated, by advances in medical science. Availability and use of prenatal care is strongly associated with improved outcome of pregnancy.⁴² Provision of adequate prenatal care for all pregnant women and reduction of adverse maternal practices requires educational and social political action.

Once an infant has been born prematurely, the prevention of bronchopulmonary dysplasia rests on preventing the development of respiratory distress. The use of exogenous surfactant as a means of preventing or decreasing the severity of respiratory distress syndrome is currently receiving considerable attention. The effectiveness of several surfactant preparations is being investigated, including those derived from calf and pig lungs, those artificially produced, and human surfactant from amniotic fluid. Comparison of different clinical trials is difficult because of differences in prophylaxis and treatment regimens, gestational ages of the subjects, composition of the exogenous surfactants, outcome measures, and insufficient identification of lung maturity.⁴³

The results from several controlled clinical trials are equivocal. Surfactant given prophylactically has decreased the incidence and severity of respiratory distress syndrome.⁴⁴⁻⁴⁸ Many trials have reported reductions in mortality and in the incidence of pulmonary air leak, and improved gas exchange.⁴³ A consistent significant reduction in the incidence of bronchopulmonary dysplasia has not, however, been shown. Surfactant seems to be a safe compound, although foreign proteins in some exogenous surfactants have the potential for activating the immune system. Sensitisation has not been shown in humans to date. Three follow

up studies have been unable to identify any long term adverse effects of surfactant treatment.⁴⁹⁻⁵¹ The exogenous surfactant preparations in use in the United States are considered to be under investigation and the most effective dose of surfactant has not been determined.

The natural antioxidant protection of premature infants may well be inadequate. Because oxygen toxicity is believed to play a part in the pathogenesis of bronchopulmonary dysplasia, the lowest concentration of supplemental oxygen that achieves an arterial oxygen tension of 8.0 kPa or greater should be used to treat the respiratory distress. Enhancing antioxidant protection with exogenous superoxide dismutase may offer some protection against developing bronchopulmonary dysplasia, but this has not yet been thoroughly evaluated. Currently it seems reasonable to attempt to maintain 'normal' levels of activity of antioxidant protection in the face of continuing supplemental oxygen challenge. Nutritional factors that contribute to antioxidant protection such as vitamin E, vitamin C, and β -carotene need to be provided as part of the management of any premature infant likely to develop bronchopulmonary dysplasia.

High frequency positive pressure ventilation, high frequency jet ventilation, and high frequency oscillation have been developed to provide artificial ventilation and reduce barotrauma. It is unclear whether any of these techniques offer any advantages over conventional mechanical ventilation in the routine treatment of respiratory failure of preterm infants. Their use does not seem to decrease the incidence of bronchopulmonary dysplasia, and may be associated with undesirable side effects such as increased incidence of grade III or IV intracranial haemorrhage.⁵²

Once the infant has developed bronchopulmonary dysplasia, bronchodilators are often used in management. Their use has been based on the clinical observation that many of these infants had bronchospasm, and infants who died of bronchopulmonary dysplasia had hypertrophied peribronchial smooth muscle.⁹ Theophylline has been shown to produce appreciable improvements in airway resistance, specific conductance, compliance, and maximal expiratory flow.⁵³ The developmental variability in theophylline clearance requires that plasma concentrations be routinely monitored and dosages adjusted. Theophylline toxicity is a concern because it has similar side effects to caffeine, and death may result from serum concentrations above 35 $\mu\text{g/ml}$.⁵⁴ β -2 Adrenergic blocking agents have also been used in the management of bronchospasm in infants with bronchopulmonary dysplasia. The use of inhaled isoproterenol has decreased airway resistance and specific conductance and decreased the work of breathing⁵⁵⁻⁵⁶; subcutaneous terbutaline, oral metaproterenol, and inhaled salbutamol have produced similar results.⁵⁷⁻⁵⁸

Accumulation of fluids may contribute to the narrowing of small airways, altered pulmonary mechanics, and impairment of gas exchange in infants with bronchopulmonary dysplasia.⁵⁹ Treatment with diuretics seems to improve lung

mechanics consistently and should decrease the work of breathing in infants with bronchopulmonary dysplasia. This effect is seen in both acute and chronic cases. Frusemide and chlorothiazide are the most commonly used diuretics, and their side effects are related to electrolyte loss in the urine and include the formation of renal calculi.

Corticosteroids have been used in the management of bronchopulmonary dysplasia during the acute, subacute, and chronic phases of the disease. Long acting corticosteroids such as dexamethasone may lead to a short term improvement in pulmonary function and facilitate weaning from mechanical ventilation.⁵⁹ Its use for as long as 42 days may improve pulmonary and neurodevelopmental outcome in VLBW infants at high risk of bronchopulmonary dysplasia.⁶⁰ The mechanism of action may be a decrease in lung oedema and polymorphonuclear infiltration and an increase in surfactant. The most serious short term side effects are increased risk of infection and hypertension, and with the long term treatment there is the potential for an increased incidence of pulmonary air leaks. Before steroids are used routinely in treating bronchopulmonary dysplasia, further data are needed regarding dose, duration of treatment, and the risk:benefit ratio.

Increasing attention is being paid to the role of nutrition of infants with bronchopulmonary dysplasia.⁶¹ Infants with bronchopulmonary dysplasia at 60 days of age have been shown to absorb energy as well as normal control infants, but they have a lower energy intake and a higher energy expenditure, which results in poor weight gain.⁶² They may also have alterations in the composition of their body tissues, with a relatively high water content. Malnutrition has deleterious effects on patients with chronic lung disease and close attention to the nutrition of infants with bronchopulmonary dysplasia is important. The effects of diuretics, gastroesophageal reflux, increased need of energy, and fluid restriction in infants with bronchopulmonary dysplasia make it difficult to provide them with adequate nutrition.

Infants with bronchopulmonary dysplasia require long periods in hospital. There is, however, an increasing tendency to develop programmes for earlier discharge of these infants while they are still dependent on supplemental oxygen.⁶³ Infants with bronchopulmonary dysplasia are susceptible to sudden infant death late in their hospital course,⁶⁴ and after discharge.⁶⁵ Before early discharge is sanctioned, there should be careful review of the infant's cardiorespiratory state and management, including the oxygen requirement, weight gain, medication regimen, and feeding plan.⁶⁶ Parental attitude plays an important part in the success of such a programme.

Bronchopulmonary dysplasia remains an appreciable problem for neonatologists. The number of children with bronchopulmonary dysplasia seen by paediatricians is increasing. These children may present with reactive airways disease, recurrent pulmonary infections, and resemble patients with asthma. Though bronchopulmonary dysplasia is thought of as a

chronic lung disease of infancy, its results may prove to be life long.

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