The role of pulmonary inflammation in the pathogenesis of BPD and potential strategies of prevention

Christian P. Speer, MD, FRCPE, University Children's Hospital, Würzburg

Increasing evidence indicates that bronchopulmonary dysplasia (BPD) results – at least in part – from an imbalance between proinflammatory and anti-inflammatory mechanisms, with a persistent imbalance that favours proinflammatory mechanisms. The inflammatory response is characterized by an accumulation of neutrophils and macrophages in the airways and pulmonary tissue of preterm infants and, moreover, by an arsenal of proinflammatory mediators which affect the alveolar capillary unit and tissue integrity. Besides proinflammatory cytokines and toxic oxygen radicals, various lipid mediators as well as potent proteases may be responsible for acute lung injury. During the last decade it has become evident that there are multiple pre- and postnatal events contributing to the development of BPD in preterm infants. Chorioamnionitis and cytokine exposure in utero, plus sequential lung injury caused by postnatal resuscitation, oxygen toxicity, volu-, barotrauma and infection all lead to a pulmonary inflammatory response which is most likely associated with aberrant wound healing and an inhibition of alveolarisation as well as vascular development in the immature lungs of very preterm infants, causing the “new BPD”.

Many strategies to prevent or ameliorate BPD have been evaluated so far (figure). Evidence for a long term preventive effect exists for the repetitive intramuscular administration of high doses of vitamin A. Oxygen supplementation remains an important therapeutic strategy for patients with established BPD. Targeting the infants at lower oxygen saturation seems to reduce long term pulmonary morbidity without significantly increasing the risk of adverse neurosensory outcome. In addition, prophylactic or very early surfactant administration in very immature infants may have a beneficial effect on the incidence of BPD. Currently there is no sufficient evidence for a routine use of iNO for the prevention of BPD. However, iNO can ameliorate oxygenation in premature infants with severe respiratory failure and might be useful in selected patients with BPD and severe pulmonary hypertension. A temporary use of diuretics can improve lung function and oxygenation in these infants. Nonetheless existing data do not justify a sustained diuretic therapy. Meta-analyses of observational studies favour a role of *U. urealyticum* in the pathogenesis of BPD. However, interpretation of results from trials of erythromycin in the prevention of the disease is hampered by small sample sizes. As the pathogenesis of disturbed alveolarization, vascularization and tissue repair in the immature lung leading to BPD is multifactorial, it is unlikely that one single agent will be
identified as a ‘miracle drug’ in the prevention or treatment of the disease. The ‘miracle drug’ of the 1990s, dexamethasone, has almost completely lost its role in the management of extremely premature infants. SOD and α1-PI have not proved to reduce the risk of moderate or severe BPD yet. Effects of other anti-inflammatory substances like intratracheal Clara Cell 10kD protein still have to be assessed in detail. The early administration of caffeine for prophylaxis and treatment of apnea of prematurity has most recently been shown to reduce the risk of BPD. This finding is surprising and promising at the same time. 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.

References


Figure. Possible pathogenetic sequence leading to BPD and interventions which have been evaluated to date.

iNo = inhaled nitric oxide, CC10 Clara Cell 10kD Protein