· Review ·

Prevention and therapy of bronchopulmonary dysplasia – evidence and clinical practice

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Abstract: The knowledge on the pathogenetic mechanisms of bronchopulmonary dysplasia (BPD) has increased considerably over recent years. However, the incidence of the disease has not substantially been changed by our therapeutic approaches. This review summarizes the existing evidence for a number of respiratory and medical strategies to prevent or ameliorate the disease and gives recommendations for clinical practice. Oxygen plays an important pathogenetic and therapeutic role for BPD. Targeting infants at lower oxygen saturation levels than traditionally used seems to confer major advantages. There is no sufficient evidence for a routine use of respiratory strategies like permissive hypercapnia or inhaled nitric oxide to prevent BPD. Diuretics can ameliorate lung function transiently. High intramuscular doses of vitamin A can reduce the risk of BPD. Early or prophylactic surfactant might also be advantageous. Postnatal corticosteroids are effective but, due to their severe side effects, should be restricted to the severest cases. Alpha1-proteinase inhibitor and superoxide dismutase have no proven benefits for BPD. The role of erythromycin has not been completely elucidated yet. Innovative strategies like Clara Cell 10kD protein still have to be assessed in future trials.

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Introduction

Although our insights into the pathogenesis and epidemiology of bronchopulmonary dysplasia (BPD) have expanded considerably in recent years[1], most of the therapies used in the management of this disease are still not evidence-based. Advances in the perinatal-neonatal management of extremely low birth weight (ELBW) infants, including prenatal steroids and postnatal surfactant, have significantly improved survival of these patients. With the increased survival rate of this high risk group the incidence of BPD has not substantially decreased over the last two decades. In this review we focus on a number of preventive and therapeutic options for patients at risk of or with established BPD. We discuss the existing evidence for the different strategies and give treatment recommendations, where ever possible.

Definitions of BPD and impact on the incidence of the disease

Since its first description in 1967 the definition of BPD has been modified several times[2-4]. Inconsistent use of this definition has hampered the comparison of the disease incidence between neonatal centers as well as the interpretation of research results. The confusion has been increased by the introduction of the unspecific term "chronic lung disease of infancy" (CLDI) which is often used interchangeably with the term BPD [5].

In 2000 a consensus conference of the National Institute of Child Health and Human Development (NICHD) refined the definition [5] (Figure 1). According to this new set of criteria, infants with a gestational age of less than 32 weeks who need supplemental oxygen for at least 28 days suffer from BPD. Depending on the degree of respiratory support or oxygen therapy at 36 weeks of postmenstrual age the disease is classified as mild, moderate or severe. Recently, it was demonstrated in a large cohort of ELBW infants that the

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severity of BPD identified by the consensus definition corresponded with the rate of adverse pulmonary and neurodevelopmental outcomes by the age of 18 to 22 months [6]. However, the application of the criteria does not reduce the differences in the reported BPD incidence between neonatal intensive care units as there is no standardization of methods for assessing the need for supplemental oxygen [7, 8]. Moreover, there is no consensus, at what oxygen saturation extremely premature infants should be targeted, and there is a wide variation in the use of oxygen for treatment and prophylaxis of other diseases like apnea or retinopathy of prematurity (ROP) [9].

Walsh and colleagues [8] recently proposed a "physiologic" definition of BPD based on a timed room-air challenge in selected infants at 36 ± 1 weeks postmenstrual age (Figure 1). According to their definition, neonates on positive pressure support or receiving > 30% oxygen at the time of assessment are assigned the outcome BPD. Those with < 30% oxygen undergo a stepwise reduction in supplemental oxygen to room air under continuous oxygen saturation monitoring. In a multicenter study including 1 598 infants with a birth weight < 1 250 g the lower oxygen saturation threshold during the room air challenge was defined as 90% over a period of at least 30 minutes [7]. BPD was diagnosed in 398 (25%) infants compared to 560 (35%) according to the traditional criterion of supplemental oxygen at 36 weeks postmenstrual age [4]. This reduction of the "incidence" of the disease by 10%, simply by using different disease definitions, is comparable to therapeutic effects reported from large randomized controlled trials addressing measures to prevent BPD [10].

The future application of Walsh's "physiologic" definition might make the diagnosis of BPD more precise in such trials. However, it only modestly influenced the variations in the reported incidence between the 17 centers participating in the multicenter study [7]. The reported rates of BPD were between 15% and 66% using the traditional definition and between 9% and 57% using the "physiologic" definition. This finding suggests that other treatment variables might contribute to these variations.

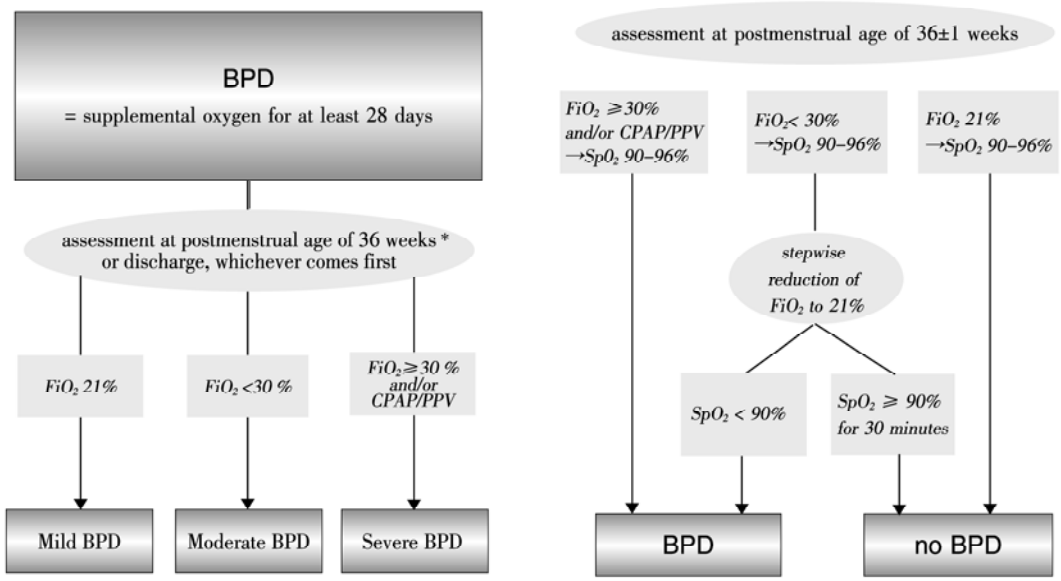

Figure 1 Comparison of the definition according to the consensus conference of the National Institute of Child Health and Human Development [left] and the "physiologic" definition of Walsh and colleagues [right].

Abbreviations: BPD = bronchopulmonary dysplasia; FiO_2 = fraction of inspired oxygen; CPAP = continuous positive airway pressure; PPV = positive pressure ventilation; SpO_2 = transcutaneous oxygen saturation.

* for infants with a gestational age ≥ 32 weeks: 56 days postnatal age

Oxygen therapy

Supplemental oxygen is often used in the management of extremely premature infants. However, there is no consensus among neonatologists about threshold levels of oxygen saturation (SpO_2) for these patients with their reduced intracellular anti-oxidative defence, putting them at high risk of suffering from potential detrimental effects of relative hyperoxemia [9]. Healthy preterm infants of 30 to 36 weeks GA breathing room air have oxygen saturations of 93% to 100% in the first 28 days of life and of 97% to 100% in the following month [11]. Data from these relatively mature infants do not reflect normal ranges for the BPD high risk infants born at a gestational age < 30 weeks. Oxidative stress in the initial phase of life has clearly been linked to the development of BPD [12]. Recent data on resuscitation of term newborns with 100% oxygen suggest that even short periods of hyperoxemia in early life can lead to prolonged oxidative stress in this patient group [13]. Besides, it has been shown that even short periods of such relative hyperoxemia immediately after birth can lead to a prolonged cerebral vasoconstriction in this group [14].

In a large retrospective observational study, infants with a gestational age < 27 weeks, who were kept at an SpO_2 level of 70%-90% in the first eight weeks of life, experienced a shorter period of mechanical ventilation and had a lower rate of BPD at a postmenstrual age of 36 weeks compared to infants, who were maintained at an SpO_2 of 88%-98% [15]. Targeting the extremely premature infants at lower SpO_2 levels had no negative effect on survival or major neurodevelopmental outcome at the age of one year. These data suggest that it might make sense to keep extremely premature infants at lower oxygen levels than traditionally used in the first weeks of life in order to protect them from detrimental effects of oxygen toxicity. Data from larger randomized prospective trials addressing this issue are currently missing.

Two multicenter randomized controlled trials have provided direct evidence that keeping preterm infants at higher oxygen levels beyond the first weeks of life does not result in short or long term benefits [16, 17]. The BOOST (Benefits of oxygen saturation targeting) trial assessed the long term benefits and harms of two different oxygen saturation target ranges (91%-94% vs 95%-98%) in 358 infants born at < 30 weeks GA who remained oxygen-dependent at 32 weeks postmenstrual age [16]. Targeting a higher SpO_2 range did not result in better growth or developmental benefits in infants at 12 months corrected age. In contrast, the duration of oxygen therapy, the incidence of BPD and the rate of home oxygen therapy were increased. The trial revealed only a non-significant reduction in the need for ablative retinal surgery in the group targeted at higher oxygen saturation levels.

The STOP-ROP trial, including nearly 650 infants with established prethreshold retinopathy of prematurity (ROP), directly assessed the effect of higher SpO_2 levels on progression of ROP [17]. The group with a SpO_2 target range of 96% to 99% showed a non-significantly reduced progression rate of the disease compared to the infants held at a SpO_2 of 89% to 94%, but in the latter group fewer infants experienced episodes of pneumonia or BPD exacerbations until the age of three months. Growth rates did not differ between the two groups.

Neither the STOP-ROP nor the BOOST trial has provided any evidence that keeping preterm infants at higher oxygen levels in the chronic phase of lung disease confer short or long term benefits. In contrast, both suggest an association between higher SpO_2 target ranges and impaired pulmonary outcome. Keeping extremely premature infants at SpO_2 levels in the lower nineties in this phase of life could be a logical consequence.

If a patient is considered to be ready for discharge, as he has had a sufficient weight gain for a longer time, maintains a normal body temperature fully clothed in an open bed with normal ambient temperature, shows competent suckle feeding and has not had a relevant apnea, bradycardia or oxygen desaturation for at least five days prior to discharge [18], but is not able to maintain an oxygen saturation in the proposed range, domiciliary oxygen therapy should be established [19].

Permissive hypercapnia

Two retrospective studies on preterm infants sugges-

ted an association between hypocarbia in the initial phase of life and bad pulmonary outcome [20, 21]. In the analysis of Kraybill the only independent risk factors for a need of supplemental oxygen at age 30 days in a cohort of 235 ELBW infants were male sex and low levels of the partial pressure of carbon dioxide ($PaCO_2$) at 48 hours of life [21]. Garland[20] analyzed the effect of ventilatory management before a first dose of rescue artificial surfactant in 188 preterm infants with respiratory distress syndrome. In his cohort the need of supplemental oxygen at 36 weeks postmenstrual age increased with decreasing $PaCO_2$ levels in the initial phase of life. Both studies concluded that ventilatory strategies leading to hyperventilation may increase the risk of BPD. Large tidal volumes in patient with relatively normal pulmonary compliance lead to low $PaCO_2$ levels as well as ventilator associated lung injury [22]. Permissive hypercapnia is a strategy to minimize baro- or volutrauma by allowing relatively high levels of $PaCO_2$ as long as arterial pH does not fall below a predefined minimal value, usually 7.2 or 7.25 [23]. It is often used by neonatologists and $PaCO_2$ values of 45-55 mmHg are widely accepted as safe and tolerable [24] although the limited data from randomized controlled trials do not favour this strategy [25, 26].

In a pilot study, Mariani and collcagucs randomizcd 49 mechanically ventilated infants with a birth weight <1 250 g to either permissive hypercapnia ($PaCO_2$ 45-55 mmHg, pH > 7.2) or normoventilation ($PaCO_2$ 35-45 mmHg, pH > 7.25) within the first 24 hours of life[27]. There was no significant difference in major pulmonary outcome like duration of mechanical ventilation or oxygen supplementation or need of supplemental oxygen at either day of life 28 or 36 weeks of postmenstrual age between the two groups. Carlo and colleagues[28] randomly assigned ELBW infants requiring mechanical ventilation at < 12 hours of age in a 2 × 2 factorial design to either minimal ventilation ($PaCO_2$ > 52 mmHg) or routine ventilation ($PaCO_2$ < 48 mmHg) for 10 days or until extubation and a tapered course of dexamethasone or placebo. After inclusion of 220 infants and an interim analysis the trial was stopped because of non-respiratory adverse effects in the dexamethasone group. The trial failed to show a significant difference in the primary study outcome death or BPD at 36 weeks postmenstrual age (63% vs 68%) but the need for mechanical ventilation was significantly reduced in the permissive hypercapnia group at that age (1% vs 16%). The failure to show a benefit of permissive hypercapnia in the prevention of BPD or death in this trial might be attributed to the small difference in the targeted $PaCO_2$ between the two groups.

A recently published prospective observational study on 43 VLBW infants has raised concerns regarding the use of permissive hypercapnia in the initial phase of life, as it might be associated with an increased risk of brain injury [24]. Indeed, in a small single center randomized trial including infants with a gestational age < 28 weeks, which was halted after an interim analysis because of failure to achieve the desired higher $PaCO_2$ levels in the majority of patients, there were trends to lower survival and worse neurodevelopmental outcome at a corrected age of 18-22 months in the minimal ventilation group [29]. In summary, the existing evidence does not favour the use of permissive hypercapnia in the management of ventilated extremely immature infants early in life [26].

Inhaled nitric oxide (iNO) in premature infants

The pathologic features of BPD include impaired pulmonary angiogenesis and alveolarization and an increased quantity of pulmonary arterial and airway smooth muscle [30, 31]. iNO can be used as a selective pulmonary vasodilator. It has extensively been applied in term neonates with persistent pulmonary hypertension and has been shown to ameliorate respiratory outcome in this population [32]. Data from animal models suggest that NO also plays a role in lung development and might be able to weaken detrimental effects of ongoing postnatal inflammation and barotrauma on the developing organ in preterm infants [33, 34].

Six randomized controlled trials have recently been published, addressing the question if iNO is safe and effective in premature infants with different severities of respiratory failure at different postnatal ages [35-40]. In a single center trial, including 207 infants with moderate respiratory failure in the first week of life, Schreiber

and colleagues[39] found a reduction of the outcome death or BPD with the administration of iNO (48.6% vs. 63.7%, $P=0.03$). In a more recent multicenter trial on infants with a gestational age < 32 weeks, who experienced moderate respiratory failure after surfactant within the first 48 hours of life, iNO was shown to be safe but did not influence the primary outcome of intact survival at day of life 28 [35].

Three multicenter trials randomizing infants with severe respiratory failure shortly after birth to either iNO or placebo could not find a difference in mortality or incidence of BPD [36-38]. Posthoc subgroup analysis in two of the trials revealed that iNO reduced the combined rate of death or BPD for infants with a birthweight > 1 000 g [36, 38]. However, it increased the incidence of BPD and severe intracranial hemorrhage for infants < 1 000 g in one study [36]. Ballard and colleagues randomized preterm infants to a tapering dose of iNO or placebo over 24 days in the second and third week of life [40]. iNO improved survival without BPD at a postmenstrual age of 36 weeks for those infants who were included during the second week of life.

Acute improvement of oxygenation was seen in an uncontrolled study of 33 ventilated patients with evolving BPD, who were treated with iNO for at least 7 days at a mean postnatal age of 19 days [41]. In eleven of 16 patients with severe ventilator-dependent BPD at the postnatal age of 1 to 7 month iNO for at least 72 hours also led to a significant amelioration of oxygenation [42]. Patients were treated for up to 90 days. Four of the infants, who initially responded to treatment, could be weaned off the ventilator during the intervention, and four of the eleven infants died. Small sample sizes and lack of a control groups clearly limit the conclusions that can be drawn from these two studies.

Up to date there is a lack of evidence for the efficacy of iNO as to long-term outcome, i.e. mortality or incidence of BPD, in high risk preterm infants. Thus, iNO cannot be recommended for routine use in these patients [43]. In patients with definite pulmonary hypertension secondary to BPD even a long-term application of iNO may be taken into account. Sufficient data supporting this strategy are currently missing.

Surfactant

Prophylactic application of natural surfactant has been shown to decrease mortality in extremely premature infants, but it does not reduce the incidence of BPD compared to a rescue approach [44]. However, for the natural porcine surfactant preparation poractant-alpha (CurosurfTM), a meta-analysis of three trials, including 671 infants, revealed that early administration in the delivery room reduced the severity of respiratory distress syndrome, mortality and the incidence of BPD at day 28 of life [45]. These data suggest that there might be a role for early or prophylactic surfactant treatment in the prevention of BPD.

Diuretics

The increased pulmonary microvascular permeability in the early stage of BPD leads to alveolar and interstitial lung edema. This edema can reduce lung compliance, increase airway resistance and impair gas exchange [46]. Diuretics can alter locally the ion-water transport in the lung and decrease the extracellular volume secondary to increased diuresis [46]. Both mechanisms lead to a net lung fluid reabsorption and a reduction of pulmonary edema. Besides, furosemide is able to reduce smooth muscle contractility in vitro and the administration of aerosolized diuretics has been shown to ameliorate reactive airway disease caused by various stimuli [47].

Systemic diuretics are frequently used in the treatment of developing or established BPD although evidence from controlled randomized trials supporting this widespread use is scarce [46]. A relevant number of these trials were done before the introduction of prenatal steroids and surfactant as standards in the care of premature infants. Trials included in a Cochrane Review of the effects of systemic furosemide mainly focused on short-term outcome [48]. They were able to show transient amelioration of lung function and oxygenation but failed to assess outcomes like duration of ventilatory support and oxygen supplementation, length of stay in hospital or mortality. Six trials were included in a meta-analysis concerning the use of diuretics act-

ing on the distal renal tubule in infants with BPD [49], only two of them assessed the effects of chronic (> 1 week) thiazide therapy, one in non-ventilated [50] and one in ventilated patients [51]. The meta-analysis revealed that in infants > 3 weeks of age with BPD chronic administration of thiazide and spironolactone transiently improved lung compliance and reduced the need for furosemide on clinical indications [49]. In intubated infants short term mortality was reduced [51]. So far, the only diuretic that has been administered to neonates as an aerosol in controlled trials is furosemide [52, 53]. A recent meta-analysis of eight studies concluded that in infant > 3 weeks of age, a single aerosolized dose of 1 mg/kg furosemide can transiently improve compliance without influencing tidal volume or resistance [47]. However, there is little or no evidence to support any benefit of either systemic or aerosolized diuretic administration with regards to long term respiratory outcome [47-49].

Short term use of systemic furosemide might be indicated in infants with BPD who suffer from acute fluid overload. A temporary therapy with thiazide + spironolactone for four to six weeks can be useful in infants with a severe form of BPD who show an amelioration of pulmonary function and oxygenation in response to the treatment. Since in the long term the inflammatory and edematous changes in the pulmonary interstitium of infants with BPD resolve, a chronic use of diuretics is not justified. Diuretics can cause nephrocalcinosis and aggravate osteopenia of prematurity due to a hypercalciuria and hyperphosphaturia. They induce hypokalemia and metabolic alkalosis which can lead to an unfavourable inhibition of ventilation and a further increase in $PaCO_2$ in infants with BPD. Thus, regular controls of blood gas analysis and electrolytes are mandatory in infants under diuretic therapy [46].

High dose vitamin A

Vitamin A plays a role in lung growth, alveolarization and surfactant production and is involved in repair of respiratory epithelium after injury [54, 55]. Preterm infants often have low serum or plasma concentrations of vitamin A, identified as risk factors for the development of BPD [56-58].

The effect of vitamin A supplementation on respiratory morbidity and mortality of preterm infants has been assessed in several randomized controlled trials [10, 59-61]. The earlier studies had rather small sample sizes and came to inconsistent results [62]. The largest multicenter trial revealed a small but significant risk reduction for the outcome death or BPD at a postmenstrual age of 36 weeks for ELBW infants, who were treated with an intramuscular dose of 5 000 IU of vitamin A, three times a week, for the first 28 days of life (55% vs 62%, relative risk 0.89, 95% confidence interval, 0.8-0.99)[10]. A daily oral dose of 5 000 IU vitamin A for 28 days did not prove to significantly alter the incidence of BPD or other major outcome variables [61]. A meta-analysis of seven trials, which was greatly influenced by the trial of Tyson and colleagues [10], discovered a significant risk reduction for BPD or death at a postnatal age of 28 days for infants with a birth weight < 1 500 g and a reduced risk of BPD at 36 weeks postmenstrual age for ELBW infants [62].

A once-per-week intramuscular dose of 15 000 IU vitamin A in ELBW infants was discarded after a comparison with two other regimens (either 5 000 or 10 000 IU three times a week) revealed that it did not lead to an equivalent increase of plasma retinol levels [63]. Although vitamin A has been proven to be effective in the prevention of BPD it has not been established as standard care of ELBW infants [64]. Probably many neonatologists feel that the potential harms of repetitive intramuscular injections to ELBW infants are not outweighed by the small risk reduction attributed to this approach.

Caffeine

Methylxanthines have clearly been proven to reduce the risk of apnea of prematurity and mechanical ventilation in extremely preterm infants [65]. However, there is uncertainty about long term sequelae of this therapy. A recently published large multicenter trial focused on the long term safety of caffeine in infants with a birth weight of 501-1 250 g [66, 67]. The main question of the trial was if the use of caffeine, beginning within the first 10 days of life, would increase mortality or impair neurosensory outcome at a corrected age of 18 months. This question has not been answered yet.

However, caffeine treatment has not affected mortality or brain injury of the enrolled infants before their first discharge from hospital. Moreover, caffeine reduced the incidence of BPD at a postmenstrual age of 36 weeks (36% vs 47% in the placebo group, odds ratio 0.6, 95% confidence interval, 0.5-0.8): The rate of medical treatment of patent ductus arteriosus was also significantly reduced from 38% to 29%. Caffeine therapy slowed down the weight gain during the first three weeks after randomization. This effect was not longer seen after the third week. These findings favour a role for caffeine in the prevention of BPD. Nonetheless, before definite recommendations can be made, the assessment of the long term effects has to be finished.

The role of anti-inflammatory drugs

Pre- and postnatal inflammation plays a pivotal role in the initiation of epithelial injury and lung remodelling leading to BPD [68-70]. High concentrations of free elastase, released from activated neutrophil granulocytes, can be found in ventilated preterm infants who develop BPD [71]. Elastase can degrade a variety of extracellular matrix proteins, immunoglobulins and fibrin. Its activity is usually counterbalanced by forming a complex with Alpha1-proteinase inhibitor (a1-PI), a glycoprotein synthesized by the liver. Oxidative inactivation of this protein is probably responsible for the very low levels of active a1-PI in premature infants [72].

Alpha1-proteinase inhibitor

The effects of a1-PI in preterm infants have been assessed in two randomized controlled trials [73, 74]. Stiskal and colleagues[73] randomized infants with a birth weight < 1 250 g to four doses of intravenous a1-PI or placebo in the first two weeks of life. Later, the same group compared three different dose regimens to placebo [74]. A meta-analysis of the two trials revealed a significant risk reduction for oxygen dependency at 28 days postnatal age when any doses of a1-PI were combined (relative risk 0.8, 95% confidence interval, 0.65-0.98) but failed to reveal any benefit with regards to BPD at 36 weeks postmenstrual age or other respiratory parameters like duration of oxygen support [75].

Corticosteroids

One of the potential positive effects of corticosteroids in the prevention of BPD is the decrease of neutrophil elastase activity. Three meta-analysis of randomized controlled trials have assessed the influence of early, moderately early and late systemic corticosteroid administration in the prevention of BPD [76-78]. Briefly, systemic corticosteroids can reduce the risk for BPD at either 28 days of life or 36 weeks postmenstrual age but in face of the known and potential short and long term adverse effects they should be restricted to the severest cases of BPD with a high risk of death from respiratory failure [9]. Early inhaled corticosteroids do not confer any advantages compared to systemic steroids in the prevention of BPD [79, 80]. A large multicenter randomized controlled trial of a "physiological" dose of hydrocortisone in the prevention of BPD was halted after an interim analysis yielded an increased rate of spontaneous gastrointestinal perforations in the hydrocortisone group [81]. However, the trial showed a significantly reduced mortality and increased survival without BPD of infants treated with hydrocortisone. Future investigation are necessary to tailor corticosteroid dosage, duration and preparation in extremely preterm infants with low cortisol levels [82].

New anti-inflammatory strategies

Other anti-inflammatory strategies to prevent or ameliorate BPD are currently investigated. The secretory Clara cells in the bronchi and bronchioles produce Clara Cell 10kD protein (CC10), which *in vitro* inhibits the soluble phospholipase A2 and thus reduces inflammation [83]. Intratracheal administration of recombinant human CC10 (rhCC10) led to improved oxygenation and static compliance in an animal model of neonatal lung injury [84]. There was a trend to a reduction of pulmonary inflammatory markers in bronchoalveolar lavage fluid in the animals treated with rhCC10. In a recently published phase II trial two different dose regimens of rhCC10 in ventilated infants < 1 300 g were compared to placebo [85]. The study drug was well tolerated and led to a significant reduction of tracheal aspirate neutrophil counts and protein concentrations as markers of pulmonary inflammation. The trial was not powered to show any effect on BPD. The potential effects of this specific anti-inflammatory drug on the development of the disease and the issue of optimal dosing regimens must be addressed by further larger

randomized trials.

Antioxidants

Oxygen toxicity plays a major role in the pathogenesis of BPD: Relative hyperoxia and recruitment of activated neutrophils into the alveoli lead to accumulation of free oxygen radicals, like superoxide anions, which are usually converted into oxygen and hydrogen peroxide by superoxide dismutase (SOD). Catalase and glutathione-peroxidase then catalyze the reduction of hydrogen peroxide into water. The immaturity of the intracellular enzymatic anti-oxidative defense and relative lack of glutathione make preterm infants susceptible to oxidative injury [86].

Two antioxidants have so far been evaluated for prevention or amelioration of BPD in randomized controlled trials. Ahola and colleagues[87] addressed the issue whether intravenous N-acetylcysteine (NAC) in extremely low birth weight infants is effective in the prevention of BPD . NAC is deacetylated to cysteine, the carrier of the active sulfhydryl residue in glutathione. Three hundred and ninety-one ELBW infants on mechanical ventilation or CPAP by the age of 36 hours were randomized to NAC or placebo in 10 Scandinavian neonatal centers [87]. The study drug did neither affect mortality nor BPD at the ages of 28 days or 36 postmenstrual weeks. NAC did not ameliorate lung function parameters assessed near term in 18 infants from the intervention group compared to 15 who had received placebo, either [88].

A small randomized trial on subcutaneous administration of bovine SOD in the early eighties yielded promising results [89]. In another small study the intratracheal application of recombinant human SOD (rhSOD) in two different dosages every 48 hours up to 7 doses was well tolerated and led to an increased SOD concentration in tracheal aspirate fluid and serum of extremely preterm infants [90]. Neutrophil chemotactic activitiy was significantly reduced in tracheal aspirate samples of the two intervention groups but the trial failed to show any beneficial effect of the study drug on BPD at 28 days of life or 36 weeks postmenstrual age.

Three hundred and two infants with a birth weight of 600 to 1 200 g who were mechanically ventilated and treated with surfactant for respiratory distress syndrome were randomized in a multicenter trial to receive either intratracheal rhSOD every 48 hours up to 1 month or placebo [91]. Treatment with rhSOD did neither affect BPD or death at 28 postnatal days nor at 36 postmenstrual weeks. However, until the corrected age of one year infants treated with rhSOD needed less asthma medications than those in the control group. This beneficial effect was more pronounced for infants with a gestational age < 27 weeks. In this subset of patients rhSOD also led to a significant lower rate of rehospitalization and emergency room visits after the initial discharge from hospital. Antioxidant therapy might attenuate long term pulmonary disease in the group of infants at highest risk [91], but future investigation must address this issue.

Ureaplasma urealyticum and Erythromycin

A recently published meta-analysis of 23 observational studies including more than 2 000 infants underlined that colonization with U. urealyticum is a risk factor for BPD at a postnatal age of either 28 days or 36 weeks [92]. However, the authors found a relevant inter-study variability in this association with the greatest reported effects in the earlier and smaller studies. In a prospective longitudinal single center study only a pattern of persistently positive U. urealyticum colonization for weeks was associated with BPD at either 28 days or 36 weeks [93]. This finding made the authors speculate that persistent colonization with the pathogen might result in ongoing cytokine production leading to prolonged inflammation and lung injury. Indeed, preterm infants whose airways were colonized with U. urealyticum showed a relevant inflammatory response in their airways [94, 95].

The efficacy of early administration of erythromycin in the prevention of BPD has been addressed by two small randomized trials [96, 97]. Both trials included infants < 30 weeks gestational age who were mechanically ventilated. Lyon and colleagues[97] randomized 75 infants at birth to a one-week course of either erythromycin or placebo. Only 9 of the infants were culture-positive, three in the treatment group and six in the placebo group. Jonsson and colleagues[96] randomized

29 preterm infants, who were colonized with U. urealyticum, to a 10-days course of erythromycin or placebo at a mean age of 7 days. Both studies were not able to demonstrate an effect of the study drug on the incidence of BPD at 36 weeks postmenstrual age. However, a true benefit might easily have been missed because of the small sample sizes. As a considerable number of at risk infants might be infected with U. urealyiticum in utero, leading to chronic inflammation and injury of the lung, postnatal erythromycin might come too late to interfere with an ongoing pulmonary inflammatory process [69]. A definitie conclusion regarding the effect of erythromycin cannot be drawn without further evidence from controlled randomized trials [98].

Existing evidence for strategies to prevent or treat BPD is shown in Table 1.

Table 1 Existing evidence for strategies to prevent or treat BPD

Strategies	Proven effect on BPD	Comments
Respiratory		
targeting lower SpO_2	yes	
permissive hypercapnia	no	benefits might be missed because of small differences in targeted $paCO_2$
iNO	no	application in infants with secondary pulmonary hypertension due to BPD may be considered.
Drugs		
vitamin A	yes	repetitive intramuscular injections of high doses are necessary
systemic postnatal steroids	yes	application must be restricted to severest cases of respiratory failure because of short- and long-term side effects
prophylactic surfactant	yes	effect proven only for poractant-alpha, so far
caffeine	yes	No recommendation for routine use until long-term neurosensory outcome will have been assessed
diuretics	no	proven short-term effects on lung function
N-acetylcysteine	no	
superoxide dismutase	no	
a1-proteinase inhibitor	no	meta-analysis of two randomized controlled trials yielded a small, but significant effect on oxygen dependency on day of life 28
erythromycin	no	benefit might be missed due to small sample size, postnatal erythromycin potentially too late

Recommendations for clinical practice

· Oxygen supplementation remains an important therapeutic strategy for patients with established BPD. Targeting the infants at SpO_2 levels in the lower nineties seems to reduce long term pulmonary morbidity without significantly increasing the risk of adverse neurosensory outcome.

· Currently, there is no sufficient evidence for a routine use of respiratory strategies like permissive hypercapnia and inhaled nitric oxide for the prevention of BPD.

· Early or prophylactic surfactant might not only reduce mortality but might also confer advantages with regards to long term respiratory outcome.

· A temporary use of diuretics can improve lung function and oxygenation in ELBW infants. However, existing data do not justify a sustained diuretic therapy.

· Currently, the only evidence for a long term preventive effect exists for the repetitive intramuscular administration of high doses of vitamin A. The effect of this strategy on the incidence of BPD is small and comparable to that of simply applying different definitions of the disease to identical groups of infants. The decision to administer repetitive intramuscular injections to ELBW infants should be based on a thorough evaluation of the local incidence of BPD and the potential risks of this strategy.

· The early administration of caffeine has most recently been shown to reduce the risk of BPD. However, the definite assessment of the primary outcome of the caffeine trial is needed before its routine use as a measure to prevent BPD can be recommended.

· Systemic corticosteroids are effective in the prevention of BPD. However, due to severe short term

and long term side effects, they should be restricted to the severest cases of respiratory failure with a high risk of death. Future investigation are warranted assessing benefit and harm of steroid 'substitution' in groups of infants whose cortisol levels are low.

· The anti-inflammatory agent a1-PI and the antioxidant superoxide-dismutase have not proven to reduce the risk of moderate or severe BPD.

· The role of erythromycin in the prevention BPD has not been sufficiently assessed yet. A routine use can currently not be recommended.

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