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# Prevention of bronchopulmonary dysplasia: current strategies

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**Abstract:** Bronchopulmonary dysplasia (BPD) is one of the few diseases affecting premature infants that have continued to evolve since its first description about half a century ago. The current form of BPD, a more benign and protracted respiratory failure in extremely preterm infants, is in contrast to the original presentation of severe respiratory failure with high mortality in larger premature infants. This new BPD is end result of complex interplay of various antenatal and postnatal factors causing lung injury and subsequent abnormal repair leading to altered alveolar and vascular development. The change in clinical and pathologic picture of BPD over time has resulted in new challenges in developing strategies for its prevention and management. While some of these strategies like Vitamin A supplementation, caffeine and volume targeted ventilation have stood the test of time, others like postnatal steroids are being reexamined with great interest in last few years. It is quite clear that BPD is unlikely to be eliminated unless some miraculous strategy cures prematurity. The future of BPD prevention will probably be a combination of antenatal and postnatal strategies acting on multiple pathways to minimize lung injury and abnormal repair as well as promote normal alveolar and vascular development. **[Chin J Contemp Pediatr, 2017, 19(8): 841-851]**

**Key words:** Bronchopulmonary dysplasia; Prevention; Strategy; Premature infant

## Introduction

Bronchopulmonary dysplasia (BPD) is a chronic respiratory condition resulting from injury to the developing lung and pulmonary vasculature of premature infants. About half a century ago, Northway et al [1] first described BPD in relatively large preterm infants with severe respiratory failure after exposure to high oxygen and ventilator pressures. With the advancements in neonatal medicine and improved survival of extremely premature infants, the clinical presentation of BPD has evolved significantly. Nowadays, BPD more commonly presents in extremely preterm infants with a milder but protracted course[2].

This continued evolution of clinical and pathologic picture of BPD and change in at risk population has brought in new challenges in developing effective prevention or treatment strategies for BPD. Antenatally, many of the factors that result in preterm delivery have been shown to adversely affect in utero development of lung and pulmonary vasculature. After birth, these infants are exposed to multiple iatrogenic and environmental factors that are injurious to the lung and pulmonary vasculature and result in maldevelopment and abnormal repair. Therefore effective prevention of BPD requires a multipronged strategy combining ways to limit lung and vascular injury and promoting normal development. Over the years multiple strategies have been tried for prevention of BPD with a variable degree of success. Some of these strategies are discussed here in more details.

## Antenatal strategies

Prematurity is the prerequisite for development of BPD, hence any strategy which can decrease the

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incidence of prematurity will lead to reduction in BPD. Unfortunately, efforts to decrease the incidence of preterm birth have not been very successful and the high incidence of preterm birth persists[3-4].

Antenatal corticosteroids have been used to promote maturation of the surfactant system and have been shown to reduce the incidence of respiratory distress syndrome (RDS). However, use of antenatal corticosteroid treatment has not resulted in reduction in incidence of BPD, partly due to improved survival of extremely premature infants at increased risk of BPD[5].

The association between chorioamnionitis and BPD has been studied extensively over the last two decades with conflicting results. In one of the earlier studies, Watterberg et al[6] reported that histologic chorioamnionitis is associated with decreased risk of RDS but increased incidence of BPD. Recently, some of the studies have failed to show association between chorioamnionitis and BPD[7]. These conflicting results may be explained by different criteria for diagnosis of chorioamnionitis, effect of other antenatal and postnatal therapies like antenatal steroids, as well as baseline incidence of BPD in the study population.

## Postnatal strategies

### Respiratory support at birth

The majority of extremely preterm infants require respiratory support in the form of positive pressure ventilation and or oxygen administration at birth. Though necessary for successful transition to postnatal life, if not provided judiciously both may lead to lung injury.

Though there is significant evidence from animal studies that even a brief period of ventilation with large tidal volumes at birth may result in significant lung injury, there are no RCTs evaluating the effect of ventilation monitoring and volume targeted ventilation during resuscitation on BPD in premature infants[8].

A strategy that has been extensively evaluated is sustained inflation of initial positive pressure breaths to help establishing a normal functional residual capacity in the lung. Despite some improvement in short term outcomes, these trials have not shown a reduction in the incidence of BPD[9]. A large multicentric RCT is currently being conducted by NICHD to evaluate the effect of this strategy on BPD. Until the results become available this strategy cannot be recommended[10].

Oxygen is one of the factors implicated in the pathogenesis of BPD. There is evidence that use of 100% oxygen during resuscitation can result in lung injury. There are limited and inconsistent data on the effects of low or high oxygen use at birth in premature infants. A recent meta-analysis of these trials failed to show a significant reduction in BPD with use of low oxygen ($FiO_2 \leq 0.3$) in comparison to high oxygen ($FiO_2 \geq 0.6$)[11]. Interestingly, some of the recent studies have shown a trend towards higher mortality in low oxygen groups when compared to high oxygen[12-13]. There is an urgent need for larger well-designed studies evaluating long-term outcomes. Until then judicious use of oxygen avoiding severe hyperoxemia and hypoxemia with continuous oxygen saturation monitoring is the most prudent approach.

### Surfactant treatment

Exogenous surfactant replacement therapy for treatment of RDS has been shown to decrease mortality, severity of RDS and the need for aggressive ventilation, but it has failed to show reduction in incidence of BPD in survivors[14]. Up till recently, one of the prerequisite for surfactant treatment has been need for endotracheal intubation and positive pressure ventilation, increasing the risk of lung injury and BPD. In the last decade, there has been a growing interest in developing minimally invasive modes of surfactant instillation like, nebulization or less invasive surfactant administration (LISA). Though these techniques need to be further evaluated in large RCTs, there is some preliminary evidence that the use of these techniques may result in decrease in the incidence of BPD[15].

Since mechanical ventilation may lead to

inactivation of endogenous surfactant, one of the strategies of interest has been the late use of surfactant in infants requiring prolonged mechanical ventilation and its effect on BPD. Recently, two large RCTs evaluated single or multiple doses of surfactant in preterm infants on mechanical ventilation for 1-2 weeks after birth and failed to show reduction in incidence of BPD with use of late surfactant[16-17].

## Noninvasive respiratory support

Since lung injury due to respiratory support is one of the major contributing factors for development of BPD, the use of least amount of respiratory support to provide adequate gas exchange has been one of the key strategies for the prevention of BPD. The various alternatives for invasive mechanical ventilation that have been evaluated are nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV) and, more recently, high flow nasal cannula (HFNC).

Since first reported by Avery et al[18], who described low incidence of BPD in centers with high use of NCPAP and avoidance of mechanical ventilation, multiple RCTs have compared the early use of NCPAP with mechanical ventilation for decreasing the incidence of BPD[19]. Though most of these trial individually have failed to show a significant decrease in the incidence of BPD with early use of NCPAP when compared to mechanical ventilation, a recent meta-analysis of studies evaluating strategies to avoid endotracheal mechanical ventilation did show a small but statistically significant reduction in incidence of BPD or death (*OR*: 0.83; *CI*: 0.71-0.96) by avoiding invasive mechanical ventilation[20].

A large number of extremely premature infants who are at most risk of BPD have been shown to fail NCPAP and require endotracheal intubation[19]. This has resulted in evaluation of NIPPV as an intermediate between NCPAP and invasive mechanical ventilation both as primary mode of respiratory support and post extubation. In some of the earlier trials, NIPPV as initial mode of respiratory support resulted in decreased incidence of BPD, but it has not been a consistent finding with recent larger RCTs failing to show a significant difference between NCPAP and NIPPV[21-23]. As a post extubation respiratory support, NIPPV has been consistently shown to be more effective than NCPAP in prevention of extubation failure with no significant effect on BPD[24].

Use of HFNC has increased significantly during the last decade, both as primary mode of support as well as post extubation, largely due to ease of use and less risk of injury to nares when compared to NCPAP. Most of the RCTs comparing HFNC and NCPAP have been performed in infants greater than 28 weeks, and have shown similar or trend towards increased incidence of BPD with use of HFNC[25-26]. A recent RCT comparing HFNC and NCPAP as primary mode of respiratory support in preterm infants of greater than 28 weeks of gestation and RDS showed increased incidence of treatment failure in HFNC group as compared to NCPAP group (Risk difference 12.3%; *CI*: 5.8-18.7; $P<0.001$)[27]. There is no data on its use as primary mode of respiratory support in extremely preterm infants.

## Strategies to reduce mechanical ventilator associated injury

Despite best efforts of clinicians, a significant number of preterm infants require invasive mechanical ventilation thereby increasing the risk of lung injury and BPD. Over the years multiple approaches have been evaluated to minimize the risk of ventilator associated lung injury.

One possible way to limit lung injury secondary to positive pressure ventilation is permissive hypercapnia. This has been evaluated in multiple RCTs with no clear effect on BPD. Unexpectedly, a recent large RCT with 362 extremely low birth weight infants showed a trend towards increased incidence of BPD or death in the group with permissive hypercapnia (36% vs 30%; $P=0.18$) as compared to control group[28].

Different modes of mechanical ventilation have been evaluated in order to find ways to provide adequate gas exchange with minimal lung injury. One

of them has been high frequency oscillatory ventilation (HFOV), which has been evaluated in multiple large randomized controlled trials with inconsistent results on the incidence of BPD. A recent meta-analysis combining these trials showed a small reduction in incidence of BPD with elective use of HFOV when compared to conventional ventilation (*RR*: 0.86; *CI*: 0.78 -0.96)[29]. Some of the reasons for the inconsistent results between trials include variation in strategies of ventilation, different patient population and use of different types of ventilators among different trials.

Since inadequate and excessive tidal volumes can play a role in lung injury, there is increasing interest in volume-targeted modes of ventilation. The comparison of volume targeted and pressure limited modes of ventilation has been evaluated in multiple RCTs. Though most of these trials were not powered enough for long term outcomes and used different methods for volume targeting, a meta-analysis combining all these trials showed reduction in combined outcome of BPD or death with the use of volume targeting modes[30].

There is clear association between duration of mechanical ventilation and incidence of BPD, therefore any strategy to expedite weaning and removal from mechanical ventilation should decrease the incidence of BPD. There is some evidence that use of weaning protocols leads to reduction in duration of ventilation but the effect on BPD has not been evaluated so far[31].

## Oxygen therapy and BPD

Oxygen, the most commonly used drug in the neonatal ICU, is on one hand life saving but on the other its injudicious use may lead to lung as well as other organ injury. The amount of oxygen to be given is titrated according to the target arterial oxygen saturation ($SpO_2$) range. The quest to find optimal target $SpO_2$ range resulted in one of the biggest undertakings in the field of neonatal-perinatal medicine with three large randomized controlled trials enrolling more than 5 000 premature infants. These trials compared the effects of two different oxygen saturation targets, low (85%-89%) and high (91%-95%) on neonatal morbidities and mortality[32-34]. Two of these trials showed significant reduction in the incidence of BPD with use of low $SpO_2$ targets[32-33]. More importantly, one of the trials showed a significant increase in mortality in the low $SpO_2$ group when compared to the high $SpO_2$ group (19.9% vs 16.2%; *OR*: 1.27; *CI*: 1.01-1.6), which was confirmed by the meta-analysis of three trials[32,35].

Despite the best efforts to maintain premature infants in the target $SpO_2$ range, these infants spend a large proportion of time outside the intended range with periods of hyperoxemia and hypoxemia. The different tools that have been evaluated to improve oxygen targeting include volume guarantee ventilation for reduction of hypoxemia episodes or automated regulation of inspired oxygen using “closed loop” systems with some short-term success[36-37]. The effect of these strategies on longer-term outcomes like BPD still needs to be evaluated.

## Management of patent ductus arteriosus

Despite significant evidence linking persistent left to right shunting from patent ductus arteriosus (PDA) to lung injury in animal models, there is paucity of clinical evidence for its role in development of BPD. The management of the PDA is one of the most controversial topics with considerable variation in practice over time and across different centers[38].

There is some evidence that delayed closure of PDA when compared to early closure may not result in adverse respiratory outcomes[39]. In addition, controversies in defining hemodynamic or clinically significant PDA, spontaneous closure of PDA in a large proportion of infants, and inconsistent success rates with significant side effects of current treatment options are some of the reasons for prophylactic or early closure of every PDA falling out of favor.

There is an urgent need to develop safer and effective treatment for PDA. Until then treatment of PDA is very likely to continue to be individualized based on each patient clinical condition and physician preference.

### Nutrition and fluid management

Postnatal growth failure is common in infants at high risk of developing BPD. The reasons for inadequate growth in these infants include a combination of failure to provide sufficient nutrition and adverse effects of some of the therapeutic interventions such as systemic steroids and diuretics used for treatment of the lung disease[40]. There is some evidence from animal models that undernutrition is associated with impaired lung growth[41] and may increase the risk of BPD independent of the severity of early respiratory failure[42].

Use of maternal milk has been associated with reduction in incidence of BPD, possibly secondary to its antioxidant properties[43-44]. Though there is paucity of large clinical trials evaluating different nutritional approaches for the prevention of BPD, a nutritional strategy providing adequate macro and micronutrients and preventing postnatal growth failure has sound physiological rationale.

There is some evidence that excessive fluid intake during the first week after birth may increase the risk of PDA and BPD[45-46] likely secondary to increased fluid accumulation in the pulmonary interstitium resulting in decreased pulmonary compliance. Therefore, a nutritional strategy consisting of judicious fluid restriction while avoiding a deficit in nutrient intake during early neonatal course is prudent.

## Pharmacotherapy for prevention of BPD

### Methylxanthines

Caffeine and aminophylline are the commonest methylxanthines used for management of apnea of prematurity. Caffeine mainly acts as a competitive adenosine receptor antagonist resulting in stimulation of medullary respiratory center, increased sensitivity to carbon dioxide and stimulation of diaphragmatic contractility. Other effects on peripheral adenosine receptors are still under investigation.

Schmidt et al[47]first described the possible role of caffeine in prevention of BPD in a large RCT investigating effect of caffeine on long-term neurodevelopmental outcomes, when used for apnea of prematurity (CAP trial). In addition to the decrease in the incidence of death or survival with major neurosensory disability, the incidence of BPD was significantly lower in the caffeine group compared to placebo (36.3% vs 46.9%; $P<0.01$). Some of the possible mechanisms of this beneficial effect are the shorter duration of mechanical ventilation and the anti inflammatory or diuretic effects of caffeine.

In the last few years, there has been an increasing trend towards use of caffeine even in infants on mechanical ventilation with no risk of apnea of prematurity. The early use of caffeine in this patient population was recently evaluated in a small RCT in which use of caffeine did not show beneficial effect on duration of ventilation in the caffeine group as compared to placebo[48] . These results suggest the need for further evidence before early caffeine can be recommended in all premature infants.

### Postnatal steroids

Corticosteroids act by reducing inflammation, decreasing vascular permeability and lung edema, thereby improving lung compliance and decreasing fibrosis. After multiple reports of adverse neurodevelopmental outcomes in the late 1990s in infants who received prolonged courses of high dose dexamethasone[49], there has been a significant effort to find an optimum regimen of corticosteroid therapy without significant neurodevelopmental side effects.

Dexamethasone has been the most studied corticosteroid for prevention of BPD with both early (within seven days of birth) and late (after seven days of birth) use resulting in decreased risk of BPD. However early use has been shown to have increased risk of cerebral palsy at follow up, whereas late use did not show significant increase in long-term adverse neurodevelopmental outcomes[50-51]. Since BPD in itself is associated with adverse neurodevelopmental outcomes, a select group of patients at high risk of BPD may benefit from low dose of dexamethasone[52].

Hydrocortisone is another corticosteroid that has been evaluated for prevention of BPD due to some evidence of low potential of neurotoxic effects when compared to dexamethasone[53]. Most of the earlier trials using hydrocortisone soon after birth showed improvement in respiratory outcomes but with increased risk of gastrointestinal perforation. A recent large multicentric RCT evaluated using a lower dose of hydrocortisone in extremely preterm infants, and showed increase in survival without BPD in hydrocortisone group when compared to placebo (60% vs 51%; *OR*: 1.48; *CI*: 1.02-2.16; *P*=0.04) without increase in incidence of gastrointestinal perforation[54]. The effect of late use of hydrocortisone on BPD and neurodevelopmental outcomes in a selected group of infants with persistent respiratory failure is currently being evaluated in a large multicentric NICHD trial[55].

One of the strategies to avoid systemic side effect of steroids is the local administration, either as an inhaled form or direct tracheal instillation in combination with exogenous surfactant. Recently, a large multicentric RCT comparing early inhaled budesonide to placebo in extremely preterm infants showed a significant reduction in incidence of BPD in infants receiving budesonide, but a trend towards increased mortality in the treated group[56]. Yeh et al[57] conducted a trial comparing initial surfactant mixed with budesonide and surfactant alone for preterm infants with severe RDS. The infants receiving surfactant with budesonide had significantly lower incidence of BPD when compared to surfactant alone (42% vs 66%; *RR*: 0.58; *CI*: 0.44-0.77; *P*<0.001). These results need to be confirmed in larger trials with different patient populations and long-term neurodevelopmental follow up before surfactant with budesonide can be recommended for prevention of BPD[58].

## Vitamin A

Vitamin A and its metabolites are involved in multiple steps of lung development as well as repair of respiratory epithelium after injury[59]. Because preterm infants have low Vitamin A stores at birth, the effect of its supplementation on BPD has been evaluated in multiple trials[60]. A recent meta-analysis of ten trials showed a small reduction in incidence of BPD with Vitamin A supplementation as compared to placebo (*RR*: 0.87; *CI*: 0.77-0.99)[61]. Despite consistently showing some effect on reducing the incidence of BPD, it is not universally used due to need for frequent intramuscular injections, high cost and limited availability[62]. The efforts to explore alternative routes of administration are currently undergoing and may provide some answers in the near future[63].

## Inhaled nitric oxide

Endogenous nitric oxide is required for alveolar and vascular development and its decreased production may contribute in the pathogenesis of BPD[64]. In addition, the supplementation of low dose nitric oxide in animal models of BPD inhibits inflammation and attenuates hyperoxia induced lung injury[65].

Clinical trials evaluating inhaled nitric oxide (iNO) for prevention of BPD have produced inconsistent results with a recent systematic review showing no significant effect on incidence of BPD[66]. Some evidence suggests that iNO may have a differential effect according to race with improved outcomes in African American race as compared to others[67]. There are multiple RCTs currently underway to evaluate the effect of iNO on BPD but until they are completed its use for this indication should only be under study protocols.

## Diuretics

Pulmonary edema is a frequent finding in preterm infants with respiratory failure due to multiple factors including left to right shunting through PDA, inflammation, or lung injury. Diuretic therapy is frequently used in these patients for short-term improvement in lung compliance resulting in better ventilation and oxygenation[68]. Both systemic and inhaled diuretics have been evaluated in RCTs with no significant effect on BPD[69]. Due to the significant side effects and no clear long-term benefits, their

routine use cannot be recommended.

### Azithromycin

Because colonization of the respiratory tract with Ureaplasma has been associated with the development of BPD, the use of macrolides has been investigated for prevention of BPD[70]. A recent meta-analysis showed prophylactic use of azithromycin resulted in reduction in incidence of BPD[71], but the data on long-term safety, appropriate dosage and pharmacokinetics of azithromycin in preterm infants is still lacking. To answer these questions, there is currently a large RCT evaluating the effect of azithromycin on long-term pulmonary and neurodevelopmental outcomes underway[72].

### Emerging therapies

The growing knowledge of molecular pathways involved in alveolar and vascular development, mechanisms of lung injury and abnormal repair has opened multiple potential targets to develop innovative preventative and treatment strategies for BPD.

Clara cell protein (CC10) is a 10 KD protein secreted by non-ciliated respiratory epithelial cells with anti-inflammatory and immunomodulatory properties. Administration of recombinant human CC10 (rhCC10) has been shown to upregulate surfactant protein and vascular endothelial growth factor expression, improve lung mechanics and decrease lung injury in animal models. A pilot study using rhCC10 in premature infants demonstrated significant anti-inflammatory effect in the lung and was well tolerated[73]. There is a multi-center RCT currently undergoing to evaluate the effect of rhCC10 on BPD and other chronic respiratory morbidities[74].

Stem cells therapies are one of the most promising strategies being extensively tested for various diseases including BPD. In animal models of hyperoxia induced lung injury, mesenchymal stem cells have shown to be effective in both prevention as well as treatment of lung injury[75-76]. Prior to use in clinical practice, better understanding of its mechanism of action, safety and efficacy in preterm infants needs to be evaluated.

## Conclusions

BPD continues to be the most common chronic respiratory condition affecting preterm neonates with significant long-term associated morbidities. With the increasing knowledge of the antenatal and postnatal factors affecting alveolar and vascular development, it is quite clear that no single therapy will eradicate BPD. Rather, in most likelihood, a combination of multiple strategies acting on the various causal pathways of BPD is more likely to be the future in the prevention of BPD.

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## 附 "Prevention of bronchopulmonary dysplasia: current strategies" 一文的中文摘译

### 支气管肺发育不良的预防策略　（姚跃　摘译）

随着近代新生儿学的持续发展和极早早产儿存活率的不断改善，支气管肺发育不良（bronchopulmonary dysplasia, BPD）的定义发生了重大变化。BPD 已不再是半个世纪前 Nothway 等学者提出的因高浓度氧及高压力通气导致的严重呼吸衰竭。新 BPD 更多发生在极早早产儿中，以损伤发育中的肺及肺血管而产生程度较轻却持续的呼吸问题为表现。由于影响肺及肺血管发育的因素贯穿早产儿产前生后的整个过程，因此对新 BPD 有效的预防策略应当包含多个角度，共同促进早产儿肺及肺血管的正常发育。近年来，BPD 的预防在很多方面都取得了一定的进展，本文在此对部分策略做简单介绍。

产前糖皮质激素的应用可增加早产儿肺表面活性物质生成，减少新生儿呼吸窘迫综合征（respiratory distress syndrome, RDS）的发生，但我们并未发现其对 BPD 的预防作用。这多半由于产前使用糖皮质激素明显增加了具有 BPD 高危风险的极早早产儿的存活率。绒毛膜羊膜炎的预防及治疗与 BPD 发生之间的关系目前仍存在争议。

早产儿窒息复苏中氧浓度的选择与 BPD 发生率的关系仍无定论，在新的可靠的证据发表前，窒息复苏中选择适中的氧浓度并持续进行血氧饱和度监测是当下最佳的选择。合适的经皮血氧饱和度目标区间对早产儿后续氧疗的指导意义重大。三项新生儿领域最大规模的 RCT 比较了目标经皮氧饱和度在不同区间（85%~89% vs 91%~95%）对早产儿病死率和发病率的影响。两项研究发现较低的经皮氧饱和度目标区间可显著降低 BPD 的发生，但其中一项研究同时发现病死率也明显增高。整合全部三项研究的荟萃分析，也同样证实了这样的趋势。

肺表面活性物质的应用并未减少 BPD 的发生，这可能与常规肺表面活性物质治疗需要气管插管和正压通气，而这样的操作会增加早产儿肺损伤有关。正因为此，越来越多的学者开始研究无创给予肺表面活性物质是否会减少 BPD 发生率，目前的初步结果是让人欣喜的，但仍有待更进一步的大规模 RCT 证实。此外，给予长时间机械通气的早产儿晚期补充肺表面活性物质理论上可能会减少 BPD 的发生，但基于该理论的两项 RCT 均未发现有意义的结果。

多项研究均未证实早产儿早期应用经鼻持续气道正压通气（NCPAP）可减少 BPD 的发生，但整合这些研究的荟萃分析却提示了可能的预防作用。与 NCPAP 相比，无创正压通气（NIPPV）可有效减少早产儿拔管失败的发生，但并未直接影响 BPD 发生率。无创呼吸支持首选 NIPPV 可能可减少 BPD 的发生，但这样的预防作用在近年来的数项 RCT 中并未得到证实。经鼻高流量氧疗（HFNC）是近年来研究较多的无创呼吸支持模式，目前暂无 HFNC 在极早早产儿中的研究数据，对于胎龄大于 28 周的早产儿 HFNC 对 BPD 的预防作用可能弱于 NCPAP。

允许性高碳酸血症是减少机械通气造成肺损伤的保护策略之一，但其对 BPD 的保护作用缺乏研究支持。近来的一项 RCT 显示，允许性高碳酸血症反而可能增加 BPD 的发生。最新的荟萃分析提示与压力控制通气模式相比，容量目标通气策略可能对 BPD 有预防作用。

而另一项荟萃分析则提示高频震荡通气（HFOV）也可能会减少 BPD 的发生，不过该分析纳入的研究同质性较差而缺乏足够的说服力。众所周知，机械通气上机时间与 BPD 的发生高度相关。理论上而言，任何有效的撤机策略都应当减少 BPD 的发生率，但目前该理论仍缺乏可靠的临床研究证据支持。

尽管持续左向右分流的动脉导管未必有可能对肺造成损伤，但目前缺乏其与 BPD 发生的直接证据。当下医学界对于极早早产儿动脉导管未闭的预防策略、临床症状评估、管理方案等均存在较大争议，在更全面、更有效统一的 PDA 管理方案出现前，动脉导管的管理可能仍需结合早产儿具体情况进行个体化考量。

母乳喂养可有效减少 BPD 的发生。尽管目前仍缺少大规模的临床研究证实营养策略对 BPD 的预防作用。但理论上而言，在避免过多液体摄入的前提下，通过提供充足的宏量元素和微量元素来减少早产儿生后生长迟缓的发生，从而预防 BPD 的发生是可行的。

各种药物对 BPD 的预防作用也是近年来临床研究和实践的热点。比如越来越多的新生儿医生开始在机械通气的早产儿中应用咖啡因以预防 BPD 的发生，但目前这样的做法仍缺乏强有力的循证医学证据支持。生后给予地塞米松可减少 BPD 的发生，但需警惕其对早产儿神经系统发育的影响。尽管氢化可的松对 BPD 也有预防作用，对神经系统发育的影响也弱于地塞米松，但有增加胃肠穿孔的风险。值得注意的是，已有研究证实小剂量氢化可的松在减少极早早产儿 BPD 发生的同时，并没有增加胃肠穿孔的风险。目前一项 NICHD 主持的大规模 RCT 正在探究晚期应用氢化可的松是否可以减少持续呼吸衰竭早产儿 BPD 的发生，改善其神经发育转归。有研究证实在肺表面活性物质治疗的同时，直接气管给予布地奈德，可显著减少 BPD 的发生率。但布地奈德临床应用预防 BPD 仍有待更多的研究明确其远期影响。

除甲基黄嘌呤和糖皮质激素类药物外，最新的荟萃分析提示补充维生素 A 可减少 BPD 的发生。但由于补充维生素 A 需要频繁的肌肉注射、成本较高、供应量也有限，大规模的临床应用存在诸多限制。一氧化氮对 BPD 的预防作用存在争议，而且预防效果还可能由于人种的不同而不同。利尿剂在早产儿中应用广泛，尽管其可短期改善肺顺应性，减少早产儿对呼吸支持和氧疗的依赖，但目前仍无可靠的证据证实利尿剂可降低 BPD 的发生率。早产儿解脲脲原体的呼吸道定植与 BPD 的发生相关，应用大环内脂类抗生素治疗可能可降低 BPD 的发生，但目前仍缺乏其对早产儿影响的全面评估，也缺少对合适剂量的考证。

大量动物实验证实干细胞及人克拉拉细胞蛋白（CC10）等新兴的治疗方法可改善肺损伤，理论上对 BPD 也有预防作用，但其安全性、有效性及合适的剂量仍有待进一步研究。

很显然，除非相关的研究有奇迹般的突破，否则 BPD 仍将继续威胁早产儿的健康。未来对于 BPD 的预防应是产前干预与生后治疗并重，通过多种途径减少肺损伤以及异常修复的发生，共同促进肺泡和血管的正常发育。

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