Published in final edited form as:
J Perinatol. 2014 September ; 34(9): 705–710. doi:10.1038/jp.2014.126.

A systematic review of randomized controlled trials for the prevention of bronchopulmonary dysplasia in infants

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Abstract

Objective—Bronchopulmonary dysplasia (BPD) is the most common cause of pulmonary morbidity in premature infants and is associated with life-long morbidities. Developing drugs for the prevention of BPD would improve public health. We sought to determine characteristics of favorable randomized controlled trials (RCTs) of drugs for BPD prevention.

Evidence review—We searched MEDLINE and EMBASE from 1992–2014 using the MeSH terms “BPD” and “respiratory distress syndrome, newborn.” We included a Cochrane Library search to ensure inclusion of all available RCTs. We identified RCTs with BPD as a primary or secondary outcome and determined the definition of BPD used by the study. We determined whether a phase I or phase II study—to determine drug safety, efficacy, or optimal dose—was performed prior to the RCT. Finally, we searched the Cochrane Library for meta-analyses for each drug and used the results of available meta-analyses to define a favorable versus unfavorable RCT.

Findings—We identified 2026 articles; 47 RCTs met our inclusion criteria encompassing 21 drugs; 5 of the drugs reduced the incidence of BPD. We found data from phase I or II studies for 16 of the drugs, but only 1 demonstrated a reduction of BPD.

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Conflict of interest

The authors declare no conflict of interest.

Financial disclosures

Dr. Cohen-Wolkowiez receives support for research from the National Institutes of Health (NIH) (1K23HD064814), the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), the Food and Drug Administration (1U01FD004858-01), the Biomedical Advanced Research and Development Authority (BARDA) (HHSO100201300009C), the nonprofit organization Thrasher Research Fund (www.thrasherresearch.org), and from industry for drug development in adults and children (www.dcri.duke.edu/research/coi.jsp). Dr. Smith receives salary support for research from the NIH, the U.S. Department of Health and Human Services, and the National Center for Advancing Translational Sciences of the NIH (DHHS-1R18AE000028-01, HHSN267200700051C, HHSN275201000003I, and UL1TR001117); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). Dr. Laughon receives support from the U.S. government for his work in pediatric and neonatal clinical pharmacology (Government Contract HHSN267200700051C, PI: Benjamin under the Best Pharmaceuticals for Children Act) and from NICHD (K23HD068497); he also receives support from Astellas, Pfizer, Abbvie, and Discovery Laboratories for his work on data safety monitoring boards and consulting. The other authors have no conflicts of interest to disclose.

Conclusions and relevance—The majority of the drugs studied in RCTs failed to reduce the incidence of BPD. Performing early-phase studies prior to phase III trials might provide necessary information on drugs and drug doses capable of preventing BPD, thus informing the development of future RCTs.

Keywords

bronchopulmonary dysplasia; randomized controlled trials; infant; newborn; FDA; labeling

Introduction

Bronchopulmonary dysplasia (BPD) is the most common cause of pulmonary morbidity in premature infants.[1] Infants with BPD are at increased risk for death, and survivors have life-long morbidities.[1–5] Despite the increased survival of extremely premature infants, BPD remains a major morbidity.[1–4,6] Approximately 40% of infants born between 22 and 28 weeks gestation are diagnosed with BPD, defined as oxygen supplementation at 36 weeks postmenstrual age (PMA).[1,5,7] Developing drugs to prevent or treat BPD, a major goal of neonatal care over the past 20 years, would substantially decrease long-term morbidity and reduce healthcare costs of premature infants.

High-quality randomized controlled trials (RCTs) are the gold standard for determining the efficacy of drugs. Over the past 20 years, multiple RCTs have examined the efficacy of drugs for prevention or treatment of BPD, but few drugs have shown favorable results.[8] Potential reasons for unfavorable RCTs include 1 or more of the following: contamination of the control group, incorrect biological basis for the intervention, variability in patient characteristics and management between centers, inadequate power to detect small effects, paucity of preliminary data, or a confounded primary outcome due to inconsistent definitions of BPD.[9]

The purpose of this systematic review was to examine RCTs of drugs for BPD prevention and determine: 1) if they were preceded by phase I and phase II (early-phase) trials, and 2) the definition of BPD used.

Methods

We followed the “Preferred reporting items for systematic reviews and meta-analyses” (PRISMA) statement for reporting of this systematic review.[10]

Search strategy

We conducted a search of the Cochrane database to identify drugs studied for BPD prevention. We used this list as MeSH terms or equivalent to compose searches of MEDLINE and EMBASE for RCTs evaluating these drugs from 1992–2014 (vitamin A, superoxide dismutase, N-acetylcysteine, nitric oxide, erythromycin, histamine antagonists, surfactants, indomethacin, bronchodilators, xanthines, cromolyn sodium, glucocorticoids, thyroid hormones, and diuretics). The search in MEDLINE included the following MeSH terms: *bronchopulmonary dysplasia* OR *respiratory distress syndrome, newborn*. We also included *chronic lung disease* as a title and abstract search term. We included search terms

for age: *infant, newborn*; and RCTs: *randomized controlled trial*. We performed an additional search to identify independent early-phase studies by substituting the RCT limitations for pilot studies: *pilot projects*. Finally, we reformatted and repeated our search in EMBASE. The search was run on March 3, 2014.

Study selection

The search was conducted by a primary reviewer (KB). We included RCTs with BPD as a primary or secondary outcome or a combined outcome of death or BPD. After title and abstract screening followed by a full-text screening, we excluded publications that evaluated modes of ventilation, routes of administration of the same drug (e.g., inhaled versus systemic), cost effectiveness, or dosing strategy comparisons.

RCT characteristics

Our review focused on the following characteristics of RCTs:

Prior early-phase studies—By examining the references of each full-text RCT, we determined whether a phase I and/or phase II study was performed prior to the RCT. A study qualified as a phase I or phase II study if the tolerability and dosing of the drug was evaluated (phase I) or if the intervention was tested for safety (phase II). Pharmacokinetic (PK) studies for appropriate dosing were also included as early-phase trials. We similarly included previous data referenced in the RCTs (not necessarily performed by the authors).

Definition of BPD—We classified definitions of BPD into 1 of 3 categories: oxygen supplementation at 28 days, O_2 at 36 weeks PMA, or the physiologic definition, described as a room air challenge between 35 and 37 weeks PMA.[11]

In addition, we searched the Food and Drug Administration (FDA) website (www.fda.gov) and other academic and professional websites (www.micromedexsolutions.com and www.dailymed.org) to obtain labeling information and determine whether a drug was FDA-approved for BPD prevention or treatment. We searched www.fda.gov to determine whether the studies were performed under an Investigational New Drug (IND) application for BPD prevention. Finally, we identified funding sources for each RCT as reported in the published study.

We summarized the characteristics of the RCTs and categorized the information based on the specific drug tested. Meta-analyses (e.g., Cochrane Collaboration) were analyzed to categorize drugs into 2 groups: drugs that prevent BPD and drugs that do not prevent BPD. If the meta-analysis found a statistically significant effect, then the drug was considered to be favorable for preventing BPD. Conversely, if the meta-analysis did not find a statistically significant effect, the drug was considered unfavorable. If there was no meta-analysis (e.g., a single study was performed), we used the risk difference as reported by the authors to determine favorability for the prevention of BPD.

Results

We identified 2026 publications for 21 drugs, including phase I and phase II studies, and phase III RCTs. We excluded 565 duplicate studies identified by both searches in MEDLINE and EMBASE leaving 1461 articles for review. After completing a title, abstract, and full-text screening, we excluded 1364 publications that did not meet our inclusion criteria. In addition, we separated 31 meta-analyses identified in the Cochrane Collaboration. Our final review included 47 RCTs and 19 early-phase studies (Figure 1). Early-phase data were referenced for 16 (76%) drugs (Table 1). A total of 11,953 infants were enrolled in the 47 RCTs. Sample sizes ranged from 26–2712 infants. A combined outcome of death or BPD was used as a primary end point in 29 (62%) RCTs. Fourteen (30%) RCTs demonstrated a reduction in BPD as either a primary or secondary outcome.

Drugs that prevent BPD

We found 13 RCTs for 5 drugs (N enrolled=4,794) that demonstrated a reduction in BPD. There was an FDA label for 3 of the 5 drugs (vitamin A, caffeine citrate, and dexamethasone) for the neonatal population, although none for the prevention of BPD (Table 1).

Vitamin A is FDA-labeled for use in prevention of vitamin A deficiency but is used off-label for prevention of BPD. Two RCTs examined the use of vitamin A for BPD prevention in 856 infants.[12,13] One trial found no difference between the incidence of BPD when infants were treated with 2000 IU intramuscular vitamin A every other day for 2 weeks versus placebo.[12] The other trial found the relative risk (RR) of death or BPD—defined either as oxygen requirement at 28 days or 36 weeks PMA—after treatment with 5000 IU intramuscular vitamin A three times a week over four weeks was 0.89 (95% confidence interval; 0.80–0.99)[13]; this study was preceded by a phase I dosing study.[14] In a meta-analysis, intramuscular vitamin A significantly reduced the incidence of BPD.[15]

Caffeine citrate is FDA-labeled for the treatment of apnea of prematurity for infants born between 28 and 33 weeks gestational age. The Caffeine for Apnea of Prematurity (CAP) trial examined 2006 infants treated with caffeine citrate for the primary composite outcome of death, cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18–21 months.[16] A secondary analysis examined additional morbidities including BPD, necrotizing enterocolitis, and retinopathy of prematurity. Infants treated with caffeine had lower risk of BPD—defined as the need for oxygen at 36 weeks PMA—than infants in the placebo group (RR=0.63 [0.52–0.73]).[16] The investigators did not perform a pilot study prior to the RCT, although they did reference prior data. However, none of the referenced data examined the PK profile of caffeine in infants. A literature review in 2012 concluded that caffeine citrate use in premature infants resulted in a significant reduction in BPD incidence with few side effects.[17]

Dexamethasone is FDA-labeled for pediatric use in various conditions, including croup and disorders of the endocrine system, but is not labeled for BPD prevention or treatment (Table 1).[18] We identified 9 RCTs examining 1513 infants treated with dexamethasone with the primary end point as BPD prevention,[19–27] while an additional trial examined 188 infants

and the incidence of chronic lung disease as a secondary end point[28]; 4 of the 10 trials used a combined end point of BPD or death. Four studies demonstrated a decrease in BPD, but only 1 used a combined outcome.[20–23] One trial was preceded directly by a pilot study[29]; however, this trial did not examine the PK or dosing profile of dexamethasone in premature infants. BPD was defined as oxygen supplementation at 28 days in 6 trials and oxygen supplementation at 36 weeks PMA in 4 trials; 2 trials used both the clinical and physiologic definitions. Several Cochrane reviews examined different dosing regimens of corticosteroids including early (<8 days), moderately early (7–14 days), and late (>7 days) administration of the drug for the prevention or treatment of BPD. The consensus suggests that, although administration of corticosteroids reduces BPD at 28 days and 36 weeks PMA, the benefit does not outweigh the risk of adverse neurological outcomes in the long term.[30–32] In 2010, the American Academy of Pediatrics re-examined the evidence for use of postnatal corticosteroids to prevent or treat BPD and concluded insufficient evidence to recommend routine use but suggested the clinician should use his or her judgment for each individual patient.[33]

We identified 2 drugs with single-center RCTs demonstrating a reduction in BPD. Inositol was studied in 233 infants with a primary outcome of survival without BPD, defined as respiratory distress at 28 days (clinical criteria for respiratory distress defined by presence of tachypnea, dyspnea, supplemental O_2 requirement, and hypercapnia)[34] and 38 weeks PMA or day of discharge; 71% of those given inositol survived without BPD compared with 55% of those given placebo (p=0.005).[35] Although inositol does not have an FDA indication for BPD because of its classification as a naturally occurring substance, it is generally recognized as safe. A recently published study also adds information regarding the pharmacokinetics of inositol in preterm infants.[36] A single trial of clarithromycin in 68 infants evaluated a primary outcome of eradication of *Ureaplasma urealyticum* and the secondary outcome of incidence of BPD, defined as oxygen requirement at 36 weeks PMA (2.9% incidence in those treated with clarithromycin vs. 36.4% in those not treated; p<0.001).[37] While clarithromycin does have FDA-labeled indications for a variety of infectious diseases, it is not approved for use in infants <6 months of age. There are no dosing data on clarithromycin for prevention of BPD. There were no meta-analyses for inositol and clarithromycin, but based on single-center studies, inositol and clarithromycin were classified as preventing BPD.

Drugs that do not reduce BPD

We found 32 RCTs for 16 drugs that did not reduce BPD. These studies enrolled 7159 infants and included surfactant, inhaled nitric oxide (iNO), selenium, hydrocortisone, allopurinol, N-acetylcysteine, inhaled beclomethasone, azithromycin, estrogen and progesterone, alpha-1-antitrypsin, inhaled salbutamol, superoxide dismutase, cromolyn sodium, inhaled fluticasone, thyroxine, and zinc (Table 1). Four RCTs of surfactant reduced the incidence of BPD.[38–41] However, meta-analyses of surfactant have not consistently supported a reduction in BPD for survivors.[42–44] While 1 trial demonstrated reductions in both the combined outcome of death or BPD (RR=0.73 [0.65–0.83]) and BPD alone (RR=0.75 [0.61–0.92]),[42] the other trial showed reductions in only the combined outcome (RR=0.89 [0.82–0.97]).[44] Although preliminary data were referenced in the surfactant trials,

these were not PK, safety, or efficacy data consistent with early-phase trials. Two of 7 iNO trials demonstrated a reduction in the incidence of BPD, but a meta-analysis did not show a reduction.[45]

Seven (16%) RCTs were preceded by early-phase studies evaluating PK and/or safety and efficacy: iNO,[46] hydrocortisone,[47] N-acetylcysteine,[48] azithromycin,[49–52] estrogen/progesterone,[53] inhaled salbutamol,[54] and superoxide dismutase.[55] Other therapeutics (inhaled beclomethasone,[56] cromolyn sodium,[57] inhaled fluticasone,[58] and zinc[59]) referenced preliminary data in their studies, but the data were not PK or safety and efficacy data.

BPD definition

Of the 47 RCTs in this review, 31 (66%) studies evaluated a combined outcome of death or BPD, defined in 1 of 3 ways: oxygen supplementation at 28 days (n=14, 45%), oxygen supplementation at 36 weeks PMA (n=22, 71%), or the physiologic definition (n=2, 6%). Four (13%) trials used both oxygen supplementation at 28 days and oxygen supplementation at 36 weeks PMA for evaluation of the primary outcome (Table 2). Only 2 trials[54,60] used the severity-based National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute workshop definition, although these manuscripts were published prior to the validation and publication of the workshop definition.[61]

Funding

We identified funding sources for 34 (72%) trials. Seven (15%) trials received funding from the FDA and/or National Institutes of Health (NIH), including vitamin A, iNO, hydrocortisone, inhaled beclomethasone, and thyroxine. Four trials on iNO were sponsored by pharmaceutical companies, and 17 trials received international funding.

Discussion

Over the past 20 years, more than 20,000 infants have been enrolled in 47 RCTs and 19 early- phase trials examining the ability of 21 drugs to prevent BPD. Only 5 drugs from 13 trials reduced BPD. Of those, only vitamin A and dexamethasone have meta-analyses demonstrating a reduction in the incidence of BPD.[15,30–32] Caffeine, inositol, and clarithromycin do not have meta-analyses due to a lack of multiple trials. Although the majority of the RCTs referenced preliminary data, few had direct early-phase studies evaluating the PK, dosing, safety, or preliminary efficacy of these drugs. In addition, the definition of BPD varied between RCTs, resulting in inconsistent primary end points across studies.

Two drugs, surfactant and iNO, were difficult to classify as favorable or unfavorable for the prevention of BPD. While 4 (50%) of the surfactant trials had favorable results, the Cochrane reviews of surfactant have not found a statistically significant difference between treatment and placebo for BPD prevention. Surfactant offers great benefit to neonates for the treatment of respiratory distress syndrome, but more trials examining the prevention of BPD should be completed. The iNO trials also have a large amount of heterogeneity, and a Cochrane review has not shown a statistically significant difference between treatment and

placebo for BPD prevention. An ongoing phase II trial through the National Heart, Lung, and Blood Institute is examining the effects of iNO on the primary outcome of incidence of BPD or death (clinicaltrials.gov: NCT00955487). Additional trials on BPD prevention, such as phase II, III, and IV trials for surfactant (clinicaltrials.gov: NCT01039285, NCT00215540, NCT01022580) and phase II and III trials for iNO (clinicaltrials.gov: NCT01503801, NCT00931632), may provide new evidence for these drugs to be classified as favorable or unfavorable for BPD prevention.

Drug development is a lengthy and expensive process. Low study consent rates and lack of consistent clinical end points make drug development in neonates particularly difficult. The typical pathway for drug approval consists of approximately 10 steps that can take years to decades to complete. After an IND application is filed and testing in human subjects is underway, phase I studies in healthy volunteers for a dosing profile are conducted, and phase II studies for efficacy in the population of interest occur before phase III trials begin.[62] Because the population in the neonatal intensive care unit is unhealthy, phase I studies are often difficult to complete. Additional barriers to enrollment in neonates include difficulty in obtaining parental consent, low prevalence of certain disease states, and the inability to separate drug effects from natural disease progression in many neonates.

Despite the number of RCTs to prevent BPD, currently no drugs are FDA-labeled for the prevention or treatment of BPD in the pediatric and neonatal population due to a lack of favorable outcomes. The lack of labeled drugs may also be because the studies were not completed under an IND, and the data were never submitted to the FDA for a label change. In response to the 1994 Pediatric Labeling Rule, the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act were established in 2002 and 2003, respectively, to increase drug studies for the pediatric population resulting in pediatric FDA labeling changes. According to an Institute of Medicine statement regarding pediatric drug studies, the therapeutic area that has the least number of drugs indicated for neonates is BPD, emphasizing the need for more safety and efficacy studies.[63] Efficacy data are often extrapolated from adult studies, assuming the pathophysiology of the disease is similar in the pediatric population and the evidence comes from an adequate number of adult studies. However, the disease process is usually different in neonates, making extrapolation difficult and often impossible. Therefore, the FDA recommends 2 adequate well-controlled trials, including a PK study, followed by an appropriate safety and efficacy study.[64–66]

Despite the difficulties researchers face when studying drugs in neonates, it is necessary to determine correct dosing in infants and children in a way similar to adult drug development.[67] Many of the trials in this review were phase III and not preceded by safety and efficacy trials or adverse event analyses. Due to the barriers encountered when attempting to enroll neonates in clinical trials, drug development is often compressed into 1 trial with safety, efficacy, dosing strategies, and adverse events analyzed simultaneously. Our results support that this method has not been successful and exposes infants to therapies that may not be safe or effective.

Successful drug development also relies on consistent definitions of the primary outcome. The definition of BPD has changed from the original definition by Northway in 1967 to the

current clinical[5] and physiologic definitions,[11] as well as the severity-based NIH workshop definition.[61] The physiologic definition provides an objective measure of oxygen dependence by performing a room air challenge at 35–37 weeks PMA. When compared with the clinical definition of BPD (oxygen supplementation at 36 weeks PMA), the physiologic definition reduced overall rates of BPD, as well as the variability among centers.[11] An NIH panel further refined the definition of BPD with a severity-based definition dependent on the amount of oxygen supplementation and respiratory support physiologically required at 36 weeks PMA. Importantly, the incidence of adverse pulmonary and neurodevelopmental outcomes increased with worsening severity of BPD.[61] Thus, the severity-based, physiologic definition objectively defines infants with moderate or severe BPD as well as identifies infants at increased risk for long-term impairment. Therefore, the severity-based, physiologic definition of BPD should be consistently used when performing RCTs evaluating a particular therapy or drug. We found the most common definition used was merely oxygen supplementation at 36 weeks PMA. However, many of these trials did not specify whether a physiological challenge was performed to confirm dependence on supplemental oxygen. Additionally, only 2 trials explicitly used the severity-based definition of BPD, although these trials were published prior to the NIH workshop definition. We understand that some trials used a clinical definition before the physiologic definition was validated in 2004, but 8 trials continued to use older clinical definitions (O_2 at 28 days or 36 weeks PMA) after the NIH workshop and the physiologic definitions were published. The use of the severity-based physiologic definition in RCTs can provide an objective measurement of impaired lung function due to BPD and decrease measurement bias across centers.[11,61]

Strengths of this review include the comprehensive nature of the search. There are currently no other published reviews examining the wide range of drugs studied to treat or prevent BPD. Study limitations include the focus on pharmaceutical therapy alone for prevention of BPD. Due to the multifactorial etiology of BPD, there are many other therapies that contribute to BPD and BPD prevention, including respiratory management (e.g., type of ventilation, oxygen exposure) and nutritional strategies. Clinical practice has changed over the last 20 years with new technologies such as high-flow nasal cannula, various nasal cannula devices, and nasal intermittent positive pressure ventilation, which all may contribute (or ameliorate) BPD physiology. Future reviews should focus on trials aimed at these alternate approaches. We also realize that we used the definitions of BPD as reported in the literature, which likely are inadequate to describe what is happening physiologically. Another limitation is the potential for publication bias. As indicated by 2 drugs with single-center RCTs, small positive trials are often reported in the literature but often unreported after expansion to a larger trial. This leads to difficulties with future drug development and information dissemination. There is a need for publication of all trials, negative or positive, supported by the pediatric community.[68]

Conclusion

The majority of RCTs of drugs for BPD prevention or treatment did not demonstrate efficacy, and currently there are no drugs FDA-labeled for BPD prevention. Performing early-phase studies (phase I and phase II) prior to phase III trials might provide important

information that can be used to identify drugs and dosing strategies capable of preventing BPD.

Acknowledgments

We would like to thank and acknowledge Kathleen McGraw for her expertise in assisting in the development of the literature search.

Funding source: This work was supported by a grant from the Doris Duke Charitable Foundation to UNC–Chapel Hill School of Medicine to fund clinical research fellow Kristyn S. Beam. The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through grant award numbers UL1TR000083 and UL1TR001117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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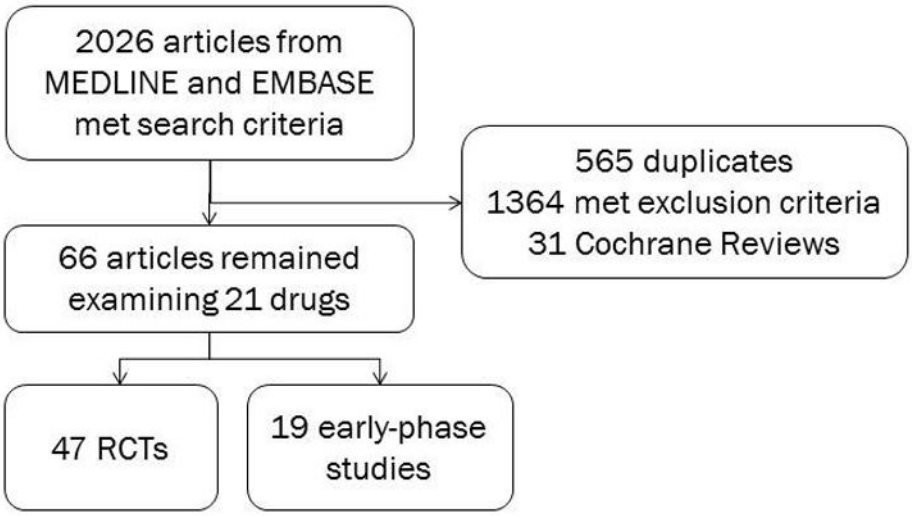

Figure 1.

Results of the literature search and article selection for randomized controlled studies of drugs for the prevention of bronchopulmonary dysplasia in infants.

J Perinatol. Author manuscript; available in PMC 2015 September 01.

Table 1

Summary of RCTs (n=47) and early-phase studies (n=19) included in review, by drug studied

	Total infants enrolled*	Infants enrolled in RCTs	Preliminary data	Prevents BPD	Favorable RCTs, N/total (%)‡	# IND/ # RCTs
Vitamin A	947	856	Y	Y	1/2 (50)	0/2
Caffeine	2006	2006	Y	Y	1/1 (100)	0/1
Dexamethasone	1671	1631	Y	Y	4/10 (40)	0/10
Inositol	233	233	Y	Y	1/1 (100)	0/1
Clarithromycin	68	68	Y	Y	1/1 (100)	0/1
Surfactant	10,128	1647†	Y	N	4/8 (50)	0/8
Inhaled nitric oxide	3092	2712	Y	N	2/7 (28)	0/7
Selenium	529	529	N	N	0/1 (0)	0/1
Hydrocortisone	451	411	Y	N	0/3 (0)	0/3
Allopurinol	400	400	N	N	0/1 (0)	0/1
N-acetylcysteine	391	391	Y	N	0/1 (0)	0/1
Inhaled beclomethasone	352	313	Y	N	0/2 (0)	0/2
Azithromycin	255	220	Y	N	0/1 (0)	0/1
Estrogen/progesterone	115	85	Y	N	0/1 (0)	0/1
Alpha-1-antitrypsin	106	106	N	N	0/1 (0)	0/1
Inhaled salbutamol	87	87	Y	N	0/1 (0)	0/1
Superoxide dismutase	59	33	Y	N	0/1 (0)	0/1
Cromolyn sodium	55	26	Y	N	0/1 (0)	0/1
Inhaled fluticasone	53	53	Y	N	0/1 (0)	0/1
Thyroxine	49	49	N	N	0/1 (0)	0/1
Zinc	97	97	Y	N	0/1 (0)	0/1
Total	**21,176**	**11,953**	**17**	**5**	**14/47 (30%)**	**0/47**

*Infants included in both RCTs and early-phase studies.

†Of the 8481 infants included in preliminary surfactant studies, 8263 were included under a treatment IND protocol for safety assessment.

‡"Favorable" defined as statistically significant results indicating a reduction in the incidence of BPD as provided in meta-analyses.

Table 2

Definition of bronchopulmonary dysplasia by trial, N = 31 (66%)*

Outcome	# RCTs
O_2 at 28 days	14
O_2 at 36 weeks PMA	22
Physiologic BPD	2
Severity-based	2
O_2 at 28 days and 36 weeks PMA	4

* Not all trials provided a definition; several trials had multiple definitions provided.