



## Mini-symposium: Secondary Pulmonary Hypertension

# Risk Factors for Development of Pulmonary Hypertension in Infants with Bronchopulmonary Dysplasia: Systematic Review and Meta-Analysis

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## EDUCATIONAL AIMS

- Bronchopulmonary dysplasia related pulmonary hypertension is a common problem.
- Identified risk factors for BPD related PHT can be categorized: perinatal, growth related, NICU stay related and demographic factors.
- Longer duration of non-CPAP ventilation, longer stay in NICU and oligohydramnios carried highest log odd ratios risk for PHT development.
- Although four different screening strategies were identified in literature, we propose a risk-factor based screening strategy for BPD induced PHT.

## ARTICLE INFO

### Keywords:

Infants  
Lung  
prematurity  
pulmonary hypertension  
risk factors  
Bronchopulmonary dysplasia  
echocardiography  
chronic lung disease

## SUMMARY

**Objectives:** Preterm infants with bronchopulmonary dysplasia (BPD) are at increased risk for development of Pulmonary Hypertension (PHT). We performed a systematic review and meta-analysis to identify risk factors for development of PHT in infants with BPD.

**Study Design:** A systematic review identified risk factors for the development of PHT in infants with BPD. A meta-analysis of the pooled data was performed for each individual risk factor.

**Result:** Of the 20 risk factors identified, 10 were repeated more than once in nine studies. Meta analysis showed that duration of mechanical ventilation, length of stay, oligohydramnios, use of high frequency ventilation, small for gestational age, sepsis and severity of BPD were significant risk factors; while birth weight and gestational age were inversely related.

**Conclusion:** Several clinical variables are predictive of the development of PHT in infants with BPD. Prospective studies are needed to transform these risk factors into a risk-based scoring system.

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## INTRODUCTION

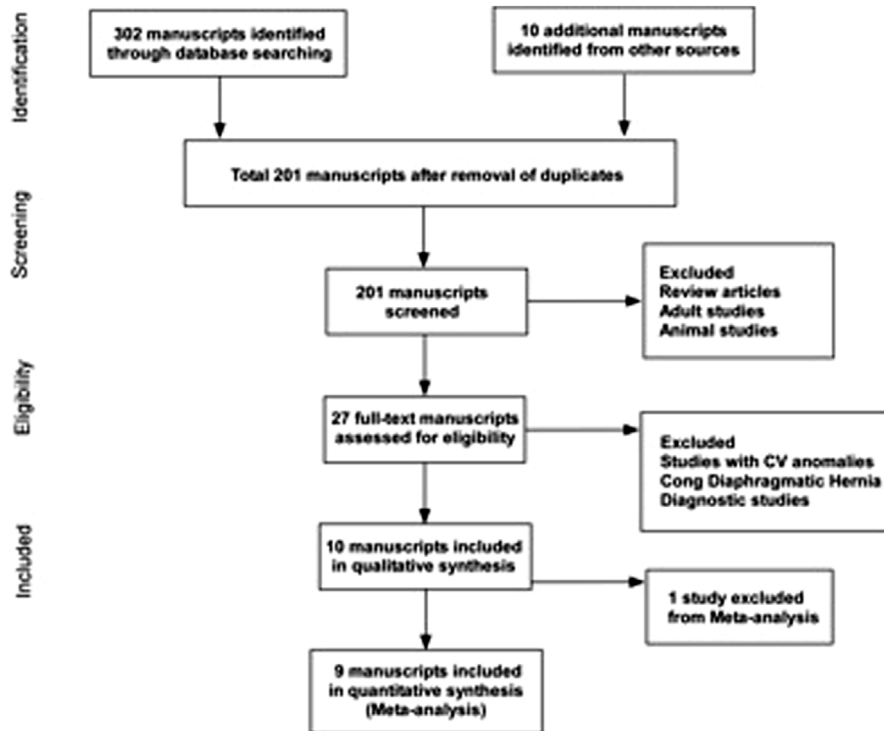
Improved rates of survival for premature infants over the last 40 years has allowed babies born with gestational ages as low as 23 weeks to survive. This improvement in survival puts an

increased number of infants at risk for the development of bronchopulmonary dysplasia (BPD), also known as chronic lung disease of prematurity. With the advances in neonatal care (surfactant use and improvements in mechanical ventilatory support), the pattern of BPD has evolved from the initial classic description by Northway et al [1]. The so-called post-surfactant era “new BPD” characterized by decreased alveolarization and compromised vasculogenesis differs from the older fibroproliferative form of BPD seen in the pre-surfactant era. Evidence shows that 18% of VLBW infants have some degree of PHT during hospitalization and this incidence increases to 25–40% in those

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Abbreviations: BPD, Bronchopulmonary Dysplasia; PHT, Pulmonary Hypertension; GA, Gestational Age; GERD, Gastroesophageal Reflux Disease.



**Figure 1.** Flowchart for screening and identification of studies for the systematic review and meta-analysis.

with established BPD [2]. Occurrence of co-existing PHT secondary to BPD has a definite impact on overall morbidity and mortality in these infants. Retrospective studies of infants with BPD-associated PHT have reported mortality rates ranging from 14 to 38% [3,4]. Several studies have examined a wide variety of risk factors for development of pulmonary hypertension in infants with BPD. Improved assessment of these risk factors might help to identify those at greatest risk for developing PHT and thereby allow us to direct adequate resources to ensure appropriate intervention and follow up. Echocardiographic screening can help to detect early cases before NICU discharge and can also guide development of an appropriate management plan based on the severity of PHT.

This systematic review analyzes the published literature to identify all the previously reported risk factors for the development of pulmonary hypertension in infants with BPD. We then performed a meta-analysis to further analyze the effect size of the risk factors, and have proposed a strategy for screening for PHT by echocardiography in infants with BPD based on these results.

## METHODS FOR LITERATURE SEARCH

We performed a systematic review of the literature using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. After identifying the research question, a literature search was conducted on 5 databases: PubMed, Scopus, CINAHL (EBSCOHost), Web of Science and Cochrane Library, using pre-defined search terms: “pulmonary hypertension”, “bronchopulmonary dysplasia”, “chronic lung disease of prematurity”, “risk factors”, “echocardiography” and “systematic review.” From the initial search results obtained from various combinations of the above search terms (Figure 1), we excluded duplicated and non-relevant manuscripts, and selected the studies that met our inclusion and exclusion criteria. This helped us to narrow down the search results to the studies that analyzed specific risk factors for PHT in BPD infants. The inclusion criteria were: Studies involving preterm infants with BPD and pulmonary hypertension (retrospective or prospective case series,

case-control studies, or intervention studies) that reported an assessment of risk factors for pulmonary hypertension. Studies were excluded if they were done in animal models, described an adult patient population, focused entirely on evaluation of diagnostic modalities, or were related to patients with cardiovascular or lung anomalies (such as congenital heart disorders or congenital diaphragmatic hernia). The description of the screening process for selection of appropriate manuscripts is described in Figure 1. Further details of the search results are also provided in the online supplement. This systematic review and meta-analysis was registered with International Prospective Register of Systematic Reviews (Protocol #CRD42015016374) (maintained by University of York Center for Reviews and Dissemination, at <http://www.crd.york.ac.uk/PROSPERO/>).

Following selection of the studies, we grouped the risk factors from all the selected papers into categories and selected the ones that were reported as a risk factor in more than one study. Using data from all the studies, a Meta analysis was performed for the selected risk factors using Comprehensive Meta analysis software (version 2, Biostat, Englewood NJ) in order to calculate log odd ratio for these risk factors. Finally, we reviewed manuscripts that have provided an approach for screening of infants with BPD for PHT using various screening strategies.

## RESULTS

### Description of the Systematic Review

The initial literature search using pre-defined search terms yielded 302 manuscripts with another 10 manuscripts identified from cross references or other sources (Figure 1). After removal of duplicates, two of the authors screened 201 manuscripts and excluded those that were review articles, pertaining to adult populations or were based on animal studies. The 27 manuscripts that included premature infants were further reviewed and a total of 17 manuscripts were further excluded as they pertained to infants with congenital heart defects, congenital diaphragmatic

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