Evidence-Based Pharmacologic Therapies for Prevention of Bronchopulmonary Dysplasia

Application of the Grading of Recommendations Assessment, Development, and Evaluation Methodology

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KEYWORDS

• Bronchopulmonary dysplasia • Chronic lung disease • Azithromycin • Caffeine
• Dexamethasone • Vitamin A

KEY POINTS

- Caffeine and vitamin A are the only pharmacologic therapies with high-quality evidence to support routine use for prevention of bronchopulmonary dysplasia (BPD) in extremely preterm infants.
- Dexamethasone is effective for the prevention of BPD but can increase the risk for neurodevelopmental impairment.
- Among extremely preterm infants at high risk for BPD, the net balance of benefits and harms may favor the use of dexamethasone after the first week of life; however, the optimal dose and duration of therapy is unknown.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) occurs in approximately 50% of extremely low-birth-weight infants, affecting 10,000 to 15,000 infants per year in the United States and accounting for more than $2.4 billion in annual health care costs.[1–3] BPD is

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associated with higher mortality rates and predisposes survivors to chronic respiratory and cardiovascular impairments, growth failure, and neurodevelopmental delay.[4–10]

The increased use of antenatal corticosteroids, surfactant therapy, and noninvasive ventilation has changed the course of lung disease associated with prematurity.[11] Once a common problem in all mechanically ventilated preterm infants, BPD is rarely seen today in bigger and more mature preterm babies with birth weights more than 1500 g.[11] In contrast, most studies suggest that BPD rates have remained stable or even increased among extremely preterm infants.[3,11–15]

Neonatal pharmacologic therapies are one important tool to reduce the burden of BPD among very immature infants. Four medications have been shown in meta-analyses or large individual randomized controlled trials (RCTs) to reduce the risk of BPD in infants born 32 weeks' gestation or earlier.[16] The authors' objective was to systematically review the evidence in support of these 4 medications (azithromycin, caffeine, dexamethasone, and vitamin A). The authors then applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess the quality of the evidence and formulate recommendations for the use of each medication.[17]

Grading of Recommendations Assessment, Development, and Evaluation Framework

The GRADE approach provides a "systematic and transparent" framework to develop clinical recommendations based on the quality of available evidence and the balance between the benefits and harms of a therapy.[17,18] The quality of the evidence in GRADE is rated as *high* to *very low* depending on the underlying study methodology and several key strengths and weaknesses that may affect the study validity.[18] RCTs begin with a *high* rating but can be downgraded because of study limitations (**Box 1**).[18] Observational studies begin with a *low* rating and can be downgraded to *very low* or upgraded to *moderate* or rarely *high* based on their strengths and weaknesses (see **Box 1**).[18]

Recommendations in GRADE are made as *strong* or *weak* and for or against the use of a therapy.[18] A strong recommendation in favor of a therapy indicates that guideline developers are confident that the desirable effects outweigh the undesirable effects.[18] In contrast, a weak recommendation in favor of a therapy implies that the guideline developers are less certain that the desirable effects outweigh the undesirable ones.[18] Most individuals should receive a therapy that is strongly recommended.[18] Much more individualized consideration of a patient's characteristics or disease state is needed when selecting the appropriate course of action in the case of a weak recommendation.[18]

METHODS

Search Strategy

The authors conducted a systematic search of PubMed from the inception of the database through 12/31/2014 for all meta-analyses, RCTs, and observational studies that assessed the efficacy of azithromycin, caffeine, dexamethasone, and vitamin A for the prevention of BPD. The search combined the individual therapy name with the following terms: *bronchopulmonary dysplasia* or *chronic lung disease*. The authors excluded case reports, editorials, letters, and non-English publications from their initial search. They reviewed the citation lists of the reviewed articles to identify additional publications for potential inclusion.