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Postnatal Corticosteroids to Prevent or to Treat Bronchopulmonary Dysplasia in Preterm Infants – CPS Podcast

Developed by Dr. Amélie Cyr and Dr. Brigitte Lemyre for PedsCases.com.
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Introduction

Hello, my name is Dr. Amélie Cyr and I am a pediatric resident at the University of Saskatchewan. This podcast was produced by PedsCases and the Canadian Pediatric Society (CPS). The goal of this podcast is to summarize the CPS Position Statement titled "Postnatal corticosteroids to prevent or to treat bronchopulmonary dysplasia in preterm infants". The podcast was developed with Drs. Brigitte Lemyre, Michael Dunn and Bernard Thébaud, the principal authors of the statement. Dr Brigitte Lemyre is a clinical investigator and an academic neonatologist at the Children's Hospital of Eastern Ontario (CHEO) and at The Ottawa Hospital, Dr. Michael Dunn is a neonatologist at Sunnybrook Health Science in Toronto and Dr. Bernard Thébaud is a senior scientist with the Ottawa Hospital Research Institute and a neonatologist at the Children's Hospital of Eastern Ontario (CHEO) and at The Ottawa Hospital. For additional information and to view the complete CPS statement, please visit www.cps.ca. The script for this podcast can be viewed at www.pedscases.com

Bronchopulmonary dysplasia (BPD) is a serious complication of preterm birth. BPD is associated with life-long respiratory and neurodevelopmental morbidity. Long-term consequences of BPD can include long-term home oxygen therapy, invasive/non-invasive ventilation, failure to thrive, and increased susceptibility to viral respiratory infections. This illness can place a huge burden on patients and families and lead to frequent hospital admissions in childhood. Advances in neonatal care have improved survival of extreme preterm infants, but unfortunately, the incidence of BPD has not decreased in the past 10 years in Canada. Given the burden of BPD, substantial research has gone into different strategies to prevent and treat it. To learn more about BPD, you could listen to a 2018 PedsCases podcast that discusses the pathophysiology, diagnosis and management BPD in more details. In this podcast, we will focus on strategies to prevent and treat BPD in the neonatal period.

Postnatal corticosteroids have been used for prevention or for treatment of BPD. However, there is considerable controversy around this therapy, and the last CPS statement on this topic published in 2012 advised against the use of postnatal

corticosteroids due to safety concerns including increased risk of cerebral palsy. The goal of this revised statement was to review studies done since the last position statement in order to guide clinicians caring for preterm infants at risk or with BPD with regards to using postnatal corticosteroids.

Objectives

By the end of this podcast, listeners should be able to:

1. Identify preterm neonates at risk of BPD
2. Highlight mechanisms leading to BPD in preterm neonates
3. Review recommendations for the use of post-natal corticosteroids to prevent or to treat BPD in preterm infants.

Case

You are working in the Neonatal Intensive Care Unit (NICU) at a tertiary care center. You just assisted to the delivery of a baby girl Olivia at 27+0 weeks gestation in the context of preterm premature rupture of membranes (PPROM) associated with chorioamnionitis. Mom did not receive adequate antenatal steroids because of precipitous labor. The baby has severe respiratory distress and is intubated soon after birth. Surfactant is administered and she is transferred to the NICU. Once she is stabilized, the team discusses the risks of BPD in this infant and whether corticosteroids should be administered to prevent or to treat it. At that time, you realize you need a bit of a refresher on what is BPD and the management strategies used.

Background and pathophysiology

Bronchopulmonary dysplasia (BPD), also known as Chronic Lung Disease (CLD) is a significant cause of mortality and morbidity in preterm infants. Many definitions for BPD exist. One definition often used is the need for supplemental oxygen at 36 weeks post-menstrual age along with respiratory symptoms and compatible changes on chest radiograph. BPD affects about 40% of babies born before 29 weeks' gestation.

There are many mechanisms involved leading to lung injury including ventilation-mediated injury and exposure to high levels of supplemental oxygen. The injuries involved in BPD lead to inflammatory responses and subsequent lung vascular and alveolar hypoplasia. Risk factors for BPD before birth include presence of chorioamnionitis and fetal growth restriction. Risk factors for BPD at birth include earlier gestational age and low-birth-weight. Finally, risk factors after birth include use of mechanical ventilation, exposure to supra-physiologic supplemental oxygen as well as sepsis and its subsequent systemic inflammatory response.

Several different management strategies can be used to prevent BPD. Those include using gentle ventilation strategies to avoid baro-volutrauma and if possible, using non-invasive respiratory supports such as CPAP or high-flow nasal cannula. We should also aim for specific saturation targets in premature babies to avoid oxygen toxicity, especially in the delivery room. Other strategies include early initiation of caffeine, which was shown to lower BPD incidence as well as optimal nutrition, which is important for normal lung

development and maturation.

Because inflammation plays an important role in the pathogenesis of BPD, corticosteroids have been used to prevent or to treat BPD. Many different regimens have been studied, showing different benefits and harms. This is still an area of active research. This statement summarizes the literature into a few categories. The first is timing – early administration in the first 7 days of life, or late administration after 7 days of life. The second is route of administration – systemic steroids or inhaled. Finally, this statement compares different types of steroids such as hydrocortisone and dexamethasone as well as different dosing regimens.

First, let's discuss the use of corticosteroids in the first 7 days of life…

Systemic corticosteroids in the first 7 days of life to prevent BPD

Based on the review of literature, the risks of dexamethasone given in the first week of life outweigh the benefits. Therefore, it is not recommended for the prevention of BPD. Risks include gastrointestinal perforations and higher risk of cerebral palsy.

More recent research has shown that physiological hydrocortisone, at replacement doses, initiated in the first 24-48 hours of life in infants born <28 weeks, when not associated with prophylactic indomethacin, increases survival without BPD at 36 weeks and survival prior to discharge without harmful effects on neurodevelopment at 2 years. High risk infants born < 28 weeks, especially those exposed to chorioamnionitis may benefit from physiological hydrocortisone at replacement dose.

Early inhaled corticosteroids to prevent BPD

Inhaled corticosteroids such as budesonide and fluticasone initiated in the first 2 weeks of life to prevent BPD are not recommended. In the studies reviewed, although the risk of BPD was decreased in the group of infants who had received early inhaled corticosteroids, they had increased death rates by 2 years. Reducing the incidence of BPD may have been achieved at the expense of increased mortality.

Next, let's discuss the research surrounding steroids after the first week of life.

Systemic corticosteroids after the first week of life to treat evolving or established BPD

There is still a need for further studies in regard to systemic corticosteroids after the first week of life. Late hydrocortisone may decrease death by 36 weeks, but there are still some safety concerns in regards to possible toxic effects. At the moment, routine use of dexamethasone or hydrocortisone for all infants who require assisted ventilation after seven days of age to treat evolving BPD is not recommended.

Ancillary analyses conducted to help guide practice for the prevention or treatment of evolving or established BPD

To help guide practice, some investigators undertook ancillary analyses to help refine

recommendations for clinical use. The summary of those analyses suggests that for a sub-group of infants at high risk of BPD, such as those who remain ventilated after the first week of life with increasing oxygen requirements and worsening lung disease, a short course of dexamethasone should be considered. The timing of initiation and initial dose should be based on postnatal age and severity of the evolving lung disease. Treatment before BPD is fully established and titration based on illness severity are advised.

Those recommendations are derived, in part, from the DART study published in 2007 that looked at a low-dose dexamethasone regimen tapered over 10 days compared to placebo in infants at risk of BPD. This low-dose dexamethasone regimen facilitated extubation and shortened the duration of intubation for ventilator-dependent infants. However, the study was stopped early. In fact, because of the low number of patients recruited, there wasn't enough power to show significant difference in death or major disability at follow-up between the treatment group and the control group. Since the DART study was published, two meta-regression studies were carried looking at the effects of dexamethasone based on the baseline risk of BPD. Those studies showed that once the risk of BPD is at least 50%, the benefits of using dexamethasone outweigh the risks associated to this intervention.

Despite the early termination of the study, the DART protocol is a commonly followed corticosteroid regimen in extremely preterm neonates. This protocol is considered in neonates who remain ventilator-dependent or who have failed previous extubation attempts. Shared decision-making with the family including explanation of risks and benefits of this treatment is essential before going ahead with this protocol.

Inhaled corticosteroids after first week of life to treat evolving or established BPD

Based on the studies done up to now, inhaled corticosteroids given between 7 and 21 days showed reduced risk of failure to extubate within 7 days. However, no difference was noted in the rate of death or BPD in infants. Therefore, at the moment, inhaled corticosteroids cannot be recommended to treat BPD and further studies are needed.

Future treatments

In terms of future treatment options, there is increasing interest in looking at corticosteroids mixed with surfactant administered via endotracheal tube early in intubated very preterm infants. Again, ongoing studies are needed to provide recommendations on this treatment option.

Back to our case:

You are back in the NICU caring for Baby girl Olivia who is now three weeks old. She is still intubated and ventilated with oxygen needs up to 40%. She had a previous failed extubation trial at 2 weeks of life. Your team members are doing all the right things in terms of lung protective strategies: they have specific oxygen targets to avoid excessive oxygen delivery, they are providing her good nutritional support and they are avoiding high pressures delivered by the ventilator. There is no evidence of ventilator acquired pneumonia or systemic infection. You are asked about the role of postnatal

corticosteroids in her management plan. You then answer that she is at high risk of BPD because she is born at less than 28 weeks and was exposed to chorioamnionitis. Considering she is at high risk of BPD and is still ventilator-dependent, we could consider a course of low-dose dexamethasone, better known as the DART protocol. The neonatologist is pleased by your answer and suggests a family meeting to explore this option with her parents. The team discusses the proposed treatment with the family, outlining the potential benefits of postnatal steroids, along with potential harms. The family engages in shared decision-making and agrees to try a course of dexamethasone. You plan to reassess her daily and remind the team to re-evaluate extubation plans on a daily basis to avoid prolonged ventilator-induced lung injury unnecessarily.

Summary

Before we leave, let's review a few key points:

1. Infants born prematurely and with low-birth weight are at increased risk of bronchopulmonary dysplasia. Excessive ventilation and supplemental oxygen lead to lung inflammation and injury. Postnatal corticosteroids have been used to prevent or treat BPD in the context of underlying inflammation.
2. You may consider a course of low-dose hydrocortisone (physiologic replacement dose) beginning in the first 24-48h after birth, for 10 days, to selected infants at the highest risk of BPD (e.g. < 28 weeks GA, exposure to chorioamnionitis). There may be an increased risk of late-onset sepsis associated with this practice. Hydrocortisone should not be combined with indomethacin prophylaxis.
3. Inhaled corticosteroids are not recommended to prevent or to treat BPD.
4. Routine use of dexamethasone after the first week of life for evolving BPD is not recommended. However, for infants still ventilated after the first week of life with increasing oxygen needs, the benefits of low-dose dexamethasone over a short course of 7-10 days outweigh the adverse effects.
5. Hydrocortisone to treat infants with evolving BPD after the first week of life is not recommended.
6. More research is needed to identify the most at-risk infants and to identify alternative corticosteroids regimens.

That concludes this podcast reviewing the Canadian Paediatric Society position statement on "Postnatal corticosteroids to prevent or to treat bronchopulmonary dysplasia in preterm infants". Thank you very much for listening!

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References:

Lemyre B, Dunn M, Thebaud B. Canadian Paediatric Sociaty, Fetus and Newborn Committee. Postnatal corticosteroids to prevent or to treat bronchopulmonary dysplasia in preterm infants. February 2020.

Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC: An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia. J Pediatr 2014;165:1258-1260.

Jefferies, A. Canadian Pediatric Society, Fetus and Newborn Committee. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. January 2017.

Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723–9.

Trembath A, Laughon MM. Predictors of bronchopulmonary dysplasia. Clin Perinatol. 2012;39(3):585–601. doi:10.1016/j.clp.2012.06.014