PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Bronchopulmonary Dysplasia.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Bronchopulmonary Dysplasia

Developed by Dr. Kevin Gipson and Dr. Anna Cook for PedsCases.com
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Introduction

Hi everyone! My name is Kevin Gipson, and I'm a pediatric pulmonology fellow at the Massachusetts General Hospital. This podcast was developed with my attending, Dr. Anna Cook, a pediatric pulmonologist at MGH, and an instructor in Pediatrics at Harvard Medical School. Our goal for today's podcast is to give you some insight into the pathophysiology and management of bronchopulmonary dysplasia or "BPD", also referred to as chronic lung disease of prematurity. BPD is an important disease in the newborn and early childhood period - affecting tens of thousands of infants annually in North America - and is an impactful contributor to morbidity and mortality in premature infants.

Many learners, myself included, find BPD to be a somewhat confusing topic during their nursery and NICU rotations. So, we'll work today to keep things straightforward and high-yield!

After listening to this podcast, the learner will be able to:

- Define bronchopulmonary dysplasia
- Describe the pathophysiology of BPD
- Discuss the evaluation and management of BPD in both the inpatient and outpatient settings
- Understand the typical outcomes for patients with BPD

We'll begin with a clinical case:

An infant girl is born at 24 and 0/7 weeks gestational age via spontaneous vaginal delivery to a G1P0 mother with an otherwise uncomplicated prenatal course. In addition to perinatal antibiotics, the mother received two doses of the steroid betamethasone on the day of delivery. The baby emerged with a weak cry, accordingly positive-pressure ventilation and supplemental oxygen is given. She is intubated at 5 minutes of life for respiratory distress and persistent desaturations, is placed on a mechanical ventilator in an SIMV mode, and is given surfactant at 15 minutes and 12 hours of life. The baby remains intubated and mechanically ventilated for the first month of her life, and despite meticulous ventilator management from the intensivist team she develops chest x-ray abnormalities concerning for patchy atelectasis and edema, and is difficult to wean from respiratory support. As a significantly premature neonate, her NICU course is further complicated by nutritional issues including the need for total parenteral nutrition, and a patent ductus arteriosus which requires surgical ligation after being refractory to indomethacin.

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Despite some early difficulties, however, this baby gradually improved with time and support from the NICU team. At one month of age she is started on a diuretic regimen, and shortly thereafter is extubated to nasal CPAP. She weans steadily to only 25cc of supplemental oxygen via nasal cannula by 3 months of age.

We'll come back to our patient's case from time to time as we discuss the pathogenesis, diagnosis, management, and outcomes of BPD.

Definitions

To begin our discussion of BPD in earnest, we should start with the basic definition of bronchopulmonary dysplasia or chronic lung disease of prematurity. First, though, a word on nomenclature. The terms bronchopulmonary dysplasia and chronic lung disease of prematurity are used synonymously in practice and in the literature. For simplicity's sake, we'll stick with the term BPD for the rest of our talk, though reasonable people disagree about which name is more descriptive. One thing to say from the outset: BPD - or chronic lung disease of prematurity - itself falls within the larger group of neonatal chronic respiratory disorders referred to as chronic lung disease of infancy or often just "CLD". As you can see, the terminology itself is frequently a stumbling block for trainees. Many of the neonatal lung diseases which fall under the umbrella term "CLD" are relatively rare, and so are outside the scope of this podcast. We'll focus on BPD as it impacts a large proportion of premature infants – many of the patients you'll be caring for on your NICU and nursery rotations.

Bronchopulmonary dysplasia is perhaps best thought of as a syndrome of lung immaturity, injury and inflammation, and a dysmature or dysregulated repair response, which leads to a persistent oxygen dependence and respiratory issues. A definition of BPD perhaps most commonly heard in the NICU and in nurseries is the constellation of clinical signs of abnormal pulmonary function, an abnormal chest x-ray consistent with BPD, exposure to positive pressure ventilation during the first week of life for a minimum of 3 days, and the need for supplemental oxygen at one month of age or 36 weeks postmenstrual age. The nature of BPD is constantly evolving, due principally to ongoing advancements which push the limits of viability for extremely premature and low birth-weight infants. As a consequence, even this already-complex definition of BPD is somewhat lacking, as it doesn't take into account the wide spectrum of prematurity and birthweight we now see in our NICUs.

Historically, BPD has been difficult to study in a consistent way, given imprecise diagnostic criteria and hospital-to-hospital variation in management strategies. In response, in 2001 an NIH working group developed refined criteria for BPD diagnoses, seeking to create meaningful subgroups of BPD which could then be used for studying interventions and outcomes. These criteria are somewhat complicated, and start by first stratifying patients by their gestational age at delivery. Patients who were less than 32 weeks GA are evaluated for BPD at either 36 weeks post-menstrual age or at time of discharge from the hospital, whichever comes first. Patients who are born at 32 weeks gestation age or later are assessed for BPD between 29 and 55 days - essentially between 1 and 2 months of age. At that time point, an infant who required oxygen supplementation for at least 28 days postnatally but whose O2 requirement has now resolved would be characterized as mild BPD. An infant who still required < 30% FiO2 would be considered moderate BPD, and a patient requiring >30% FiO2 and/or positive-pressure ventilation would have severe BPD. Pretty complicated, right? Again, though these definitions are complex, the hope is that a nuanced classification of bronchopulmonary dysplasia will help researchers better study this disease and be able to account for the spectrum of prematurity and low birth weights.

Etiology and Pathogenesis

You may have also heard the terms “old” and “new” BPD, a division which reflects an evolution in the manifestations of BPD as care for these infants has advanced over decades. While we’ll focus on “new” BPD for the remainder of this podcast, it might be helpful to talk briefly about this evolution in the pathophysiology of neonatal lung disease.

The early 1960s were a remarkable time in the field of neonatology. With the first clinical use of exogenous surfactant in the late 1950s by Dr. Mary Ellen Avery, followed shortly by the emergence of mechanical ventilation for neonates in hospitals, it was a time when premature infants with respiratory distress syndrome – a condition borne of a lack of adequate endogenous surfactant in the “premie” lung – were increasingly surviving the immediate post-natal period. The “old” BPD was first defined in the days before many of the supportive perinatal and neonatal interventions we have today – for example antenatal steroids and protective ventilator strategies – had been developed. Premature neonates with RDS were being mechanically ventilated for prolonged periods of time, with relatively high FiO2s and high peak inspiratory pressures which exposed the immature lungs to extensive barotrauma. In that context, BPD emerged as a persistent oxygen requirement and other pulmonary sequelae in that subset of premature infants who were surviving past the acute RDS phase. Lung histopathology revealed striking inflammatory and post-inflammatory changes in both the airways and parenchyma of the lungs, including heterogenous areas of both air-trapping and atelectasis, pulmonary vascular changes, and necrotizing bronchiolitis – leading Dr. W.H. Northway to call the disease “bronchopulmonary dysplasia” in order to highlight these changes in both the airways and lung parenchyma.

As neonatal management has advanced to the current state of the art, BPD has shifted to infants at increasing extremes of prematurity and low birth weight. To understand why BPD might develop in these extremely premature infants, it might be helpful to pull out your favorite human development text and review the stages of lung development. As the fields of Perinatology and Neonatology continue to lower the so-called “limit of viability”, which now hovers somewhere around 22 to 23 weeks gestational age, infants with increasingly immature lungs are being born and subsequently mechanically ventilated. The lungs of an infant born at 23 weeks gestation are still transitioning somewhere within the canilicular and saccular phases of development, characterized by formation of the pulmonary capillary bed and ongoing subdivision and growth of the structures which will ultimately mature into alveoli sometime around the 36 week mark. As a consequence, the immense disruption to pulmonary development that attends premature birth and mechanical ventilation at this critical point leads to a sort of arrest of development, and histopathology of the lungs of an infant with “new” BPD may demonstrate simplified alveoli with decreased septation and surface area, increased interstitial fibrosis, and abnormal pulmonary vasculature and poorly developed alveolar-capillary networks. There is less inflammatory cell infiltration than was seen classically in “old” BPD.

A number of perinatal and post-natal factors conspire to cause this developmental damage to the neonatal lung. As early as Dr. Northway’s first descriptions of BPD in 1967, it was suspected that exposure to high inspired FiO2 might contribute to the pathogenesis of BPD. This has indeed borne out, and it is now known that, in addition to being associated with the development of retinopathy of prematurity, excessive exposure to supra-atmospheric concentrations of supplemental O2 increases the risk of BPD in extremely preterm infants. While the mechanism is unclear, it is thought that reactive oxygen species may cause cytotoxic effects in the immature airways, and that premature infants are particularly susceptible to this due to a paucity of

antioxidant enzymes. A number of studies have shown that relative hypocapnia is associated with BPD, suggesting that over-aggressive mechanical ventilation, and likely resultant volutrauma or barotrauma, is at play in the pathogenesis of BPD. In response, neonatal intensivists and respiratory therapists have become increasingly attuned to and adept at minimizing damage to the neonatal lung by way of protective ventilator strategies including permissive hypercarbia, maintenance of adequate PEEP to minimize recurrent atelectasis, and use of non-invasive modalities including nasal CPAP. Perinatal infection, specifically chorioamnionitis, may negatively impact the premature lung by inducing a dysregulated inflammatory response through the presence of pro-inflammatory cytokines into the amniotic fluid, however studies of this hypothesis have been inconclusive. Early post-natal sepsis is associated with the development of BPD. Other potential contributors to the pathogenesis of BPD include the presence of a PDA, and a host of prenatal and antenatal factors, chiefly maternal smoking. Further, a number of studies of monozygotic and dizyotic twins suggest a possible genetic predisposition to BPD, and genome-wide association studies have identified single nucleotide polymphisms in genes encoding endothelial nitric oxide synthase. That said, no clear genetic etiology has been implicated in the development of BPD, and it is almost certain that the disease is deeply multi-factorial in its etiology.

Physical findings, imaging, and laboratory evaluation

The pulmonary exam of the premature infant can be difficult, and infants with BPD may have markedly variable exams as a consequence of the wide spectrum of disease severity and comorbid conditions seen in BPD. A quick pro-tip: it's always a great idea to speak with the baby's nurse before examining your NICU patients when possible! Neonates generally – and BPD babies specifically – can be quite tenuous, and so it's great to make sure it's an appropriate time to examine the baby. The nurse can also help you reposition the baby to facilitate the exam if necessary, which can be especially difficult if an infant is intubated. Infants with BPD will often be tachypneic and may have retractions. The chest wall diameter may be increased. If the patient is mechanically ventilated or on nasal CPAP, lung auscultation can be difficult, with lung sounds obscured by overlying mechanical noises. If you can hear breath sounds, you may hear fine rales from pulmonary edema, or wheeze if the patient has severe BPD and small airway obstruction from scarring or mucus retention. Similarly, you may be able to detect a subtly prolonged expiratory phase if there is air-trapping. Often, the lung sounds will be just coarse, or even relatively clear. The cardiac exam can be normal, or may suggest pulmonary hypertension in those patients with significant pulmonary vascular involvement.

Chest imaging is an important part of the initial diagnosis of BPD. The plain film chest x-ray evolves along with the progression of BPD, and in the "new" BPD generally appears as a diffuse, hazy interstitial pattern which can represent both pulmonary edema and later airway fibrosis. In severe cases, chest hyperinflation and air-trapping will be evident. In the presence of comorbid pulmonary hypertension, you may be able to appreciate a fullness of the pulmonary vasculature, and all patients with suspected BPD and persistent oxygen requirement should undergo screening echocardiogram to evaluate for pulmonary pressures.

In regard to lab work, infants undergoing mechanical ventilation will typically get routine arterial blood gasses. As mentioned earlier, we can use blood gasses to achieve a permissively hypercarbic state, targeting a partial pressure of arterial carbon dioxide (PaCO2) of 50 to 55 mmHg and a pH ≥7.2. Many infants with BPD are managed with diuretic medications, which we will describe in a moment. During the initial dosing and titration of these medications, as well as in outpatient follow-up, it is important to monitor the patient's electrolytes, specifically sodium, potassium, and chloride, as these can be altered significantly with diuretic use.

Management

In a premature infant at risk for developing BPD, a number of early considerations are important for mitigating the potential adverse effects of mechanical ventilation. Appropriate goal-directed ventilator management is a crucial component of BPD care. While a detailed discussion of ventilator strategies in BPD is beyond the scope of today's podcast, in broad strokes the goals of mechanical ventilation in these patients is one of minimizing barotrauma or volutrauma by careful attention to peak inspiratory pressures and tidal volumes, and by preventing atelectasis through the use of positive end-expiratory pressure. Again, the concept of permissive hypercarbia – while monitoring blood gasses for acidosis – can permit lower tidal volumes and thus minimize volutrauma. Ideally, infants with BPD or at risk for BPD should be extubated as soon as clinically feasible. Many infants can either start on nasal CPAP at time of delivery as an intubation-sparring modality, or be quickly extubated to CPAP to minimize time on the vent. Not only does early extubation minimize a patient's exposure to supra-physiologic distending pressures and volumes, but it also reduces the likelihood of developing ventilator-associated pneumonia. While most infants can ultimately extubate to CPAP or nasal cannula, some infants may require tracheostomy to facilitate long-term mechanical ventilation, and this can be a crucial intervention for the developing infant and fosters infant attachment. While tracheostomy can be a difficult decision for parents and even the medical team, tracheostomies can permit more facetime with parents and caregivers, reduced sedation, and a safer and more secure airway for infants. Infants who have a difficult time extubating to a non-invasive positive pressure modality such as CPAP may benefit from an upper airway evaluation to rule out subglottic stenosis or severe laryngomalacia or tracheomalacia as a confounding variable.

Supplemental oxygen remains a critical therapy for many patients with BPD, but specific saturation targets remain controversial. Studies of relative hypoxemia in the range of 85-91% showed some promise in reducing BPD, but had increased overall mortality. In our practice, we recommend a target SpO2 of 92-95% for most infants with uncomplicated BPD. Many infants will wean steadily on O2 support until relatively low flows of 100cc/min or less. Then, subsequent attempts to wean further in the NICU or nursery may be frustrated by intermittent desaturations, particularly during cares or when sleeping. In these cases, our practice pattern is to choose a modest level of support which minimizes the desaturation events, and then plan to discharge the baby on that level of support when otherwise clinically ready. The goal here is two-fold: First, we worry that significant intermittent desaturations might have deleterious effects on neurodevelopment. Secondly, we feel that, in marginal cases, supplemental O2 will provide the infant with "reserve" for the unavoidable normal respiratory illnesses of early childhood. Infants with supplemental O2 via nasal cannula will generally go home with pulse oximetry units, which can be helpful in guiding future outpatient weans.

Premature infants may also have immaturity of the respiratory drive, which can result in apnea of prematurity. Caffeine is not only effective in stimulating the respiratory drive of premature infants, but has also been shown to decrease the incidence of BPD in premies when given within the first 10 days of life.

As endothelial dysfunction in BPD can lead to pulmonary edema and consequent impaired pulmonary dynamics, a major pillar of the medical management of BPD is the use of diuretics, commonly the loop diuretic furosemide, the thiazide chlorothiazide, and the potassium-sparring diuretic spironolactone. We will generally start diuretics if a patient is still requiring PAP at 3-4 weeks of life. As mentioned before, these medications can lead to electrolyte derangements,

particularly when used on a long-term daily basis. Often, infants on these types of medications require supplementation with potassium chloride or sodium chloride.

Those infants found to have a patent ductus arteriosus – "PDA" - should receive a cardiology consultation, and will generally undergo a trial of indomethacin to close the PDA followed by surgical ligation if necessary. As BPD is associated with some degree of pulmonary vascular dysmaturity including endothelial smooth muscle hypertrophy and insufficient pulmonary capillary beds, some infants with severe lung disease may have comorbid pulmonary hypertension. These patients may acutely require pulmonary vasodilation inhaled nitric oxide, and in severe cases may even require extracorporeal membranous oxygenation - ECMO. Many of these children often are transitioned to the oral phosphodiesterase inhibitor sildenafil or the endothelin receptor antagonist bosentan for long-term therapy. Infants with pulmonary hypertension may benefit from screening for gastroesophageal reflux and silent aspiration.

Premature infants with BPD benefit significantly from nutritional interventions to optimize appropriate weigh gain and growth. The increased work of breathing attendant to BPD and chronic lung disease can burn significant calories, and so appropriate caloric and nutritional supplementation is critical in avoiding failure to thrive and in promoting and facilitating lung healing in this population.

Systemic steroids for the prevention and treatment of BPD remains a quite controversial subject despite numerous studies. Recent meta-analyses suggest that benefits of corticosteroid therapy, namely decreased time on mechanical ventilation and possible decreased risk of BPD in premature infants, may not outweigh potential adverse effects including concern for gastrointestinal perforation, hypertension, growth failure and adverse neurodevelopmental outcomes. Inhaled steroids have not clearly been shown to convey any efficacy advantage over systemic steroids, however further studies may ultimately show a safety advantage, as presumably there would be less systemic absorption.

Finally, infants with BPD are particularly susceptible to community acquired respiratory illnesses, particularly the slew of viral illnesses which emerge in the fall and early winter such as respiratory syncytial virus (RSV) and flu. A critical aspect of outpatient care for these at-risk infants is prophylaxis with the anti-RSV monoclonal antibody palivizumab. Current American Academy of Pediatrics and Canadian Paediatric Society guidelines, recommend that infants in their first year of life with BPD - defined somewhat strictly as those infants born at less than 32 weeks gestational age and with a requirement for >21% oxygen for at least the first 28 days after birth – receive palivizumab prophylaxis for RSV infection. For children with BPD in their second year of life, pavalizumab is recommended for those children who require ongoing medical support – for example, ongoing oxygen or diuretic therapy. The antibody is usually administered as an injected dose one month prior to the onset of RSV season – which runs from roughly late October to late January in North America – and then subsequent injections every month for the duration of the season. Similarly, patients six months of age and older, and their caregivers, should receive the seasonal flu vaccine.

Outcomes

By following these patients closely in the primary care and pulmonology clinics, monitoring for oxygen requirements, signs of failure to thrive or pulmonary hypertension, and by providing prophylaxis for RSV and seasonal *Influenza immunization*, we can safely steward these patients through their first few years of life and ensure the best possible outcomes for our patients.

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Very few patients with BPD will have an ongoing oxygen requirement by two years of age, and most patient have subjectively normal respiratory health without overt physical limitations. However, longitudinal pulmonary function testing often demonstrates persistent airflow limitation in many of these patients, and there seems to be an increased prevalence of reactive airways disease and asthma in NICU graduates with a history of BPD. Many are managed with inhaled corticosteroids and as needed bronchodilators. Patients with a history of severe BPD have an increased incidence of chronic obstructive pulmonary disease, and may benefit from anticholinergic bronchodilating medications such as tiotropium.

Returning to our case

Our patient was discharged from the hospital at around 3 months of age, on 25cc/min oxygen supplementation via nasal cannula and a scheduled dose of diuretic medication. Based on her gestational age of less than 32 weeks, and her need for ongoing oxygen supplementation < 30% FiO2 at 36 weeks postmenstrual age or time of discharge, she should be characterized as having moderate bronchopulmonary dysplasia. She follows up regularly in clinic, and by all accounts she is thriving. Her growth curves show excellent weight gain when corrected for gestational age, and she is meeting developmental milestones. Her parents monitor her oxygen levels intermittently during the day, and report that she is always >95% on the 25cc of supplemental oxygen. At the most recent pulmonary clinic visit, the decision was made to wean her from daytime oxygen. She will continue to use supplemental oxygen while asleep at night, and the parents will report back on nocturnal pulse oximetry readings in a few months. With her steady gains in weight, she has effectively outgrown her diuretic dose, and so that will also be discontinued. As the winter is approaching, she receives her first palivizumab dose in her pediatrician's office, and her parents and older siblings all get the seasonal flu vaccine. It remains to be seen whether our young patient will have any element of reactive airways disease or persistent airway obstruction as a sequel of her bronchopulmonary dysplasia, but every indication is that she will continue to thrive, and she is well on her way to becoming a happy toddler.

Conclusion

Bronchopulmonary dysplasia is an important and evolving disease of premature infants who are exposed to positive pressure ventilation in the neonatal period. It is a clinical syndrome with a spectrum of severity, and this heterogeneity of presentation makes it both a potentially confusing topic for practitioners and a difficult field of study for research. As the perinatal and neonatal management of extremely premature neonates continues to advance, the prevalence of prematurity and BPD in the newborn population is all but certain to increase. By broadening our understanding of this complex syndrome through clinical and basic research, we will work meet the challenges posed by this disease for our patients and their families.

As we end today's podcast, let's review a few important take-home points about bronchopulmonary dysplasia:

- Bronchopulmonary dysplasia is a syndrome of lung immaturity, injury and inflammation, and a dysmature repair response, which subsequently leads to a persistent oxygen dependence and respiratory issues.
- BPD is most simply defined as clinical signs of abnormal pulmonary function, an abnormal chest x-ray consistent with BPD, exposure to positive pressure ventilation during the first week of life for a minimum of 3 days, and the need for supplemental oxygen at one month of age or 36 weeks postmenstrual age. However, BPD is a

spectrum disease of significant complexity, and so more nuanced NIH criteria were developed to aid in stratification of severity in order to aid in prognosis and research.

- Mainstays of the inpatient management of BPD include protective ventilator strategies such as permissive hypercapnia and goal-oriented volume and pressure titration, minimizing excessive oxygen therapy, nutritional optimization and management of gastroesophageal reflux, and correction of comorbid issues such as a PDA and pulmonary hypertension.
- In the outpatient setting, we focus on ensuring good weight gain and prophylaxis from viral illness, while titrating diuretic and oxygen therapy as needed.
- Most children with BPD will improve clinically during the first few months of life; though in some cases there can be prolonged supplemental oxygen and diuretic requirement, and some children may have persistence of airflow abnormalities on pulmonary function testing.

That concludes our presentation. We'd like to thank Dr. Bernard Kinane of MGH and HMS for his review of this talk. **Thanks for listening to PedsCases podcasts!**

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