Managing Severe Acute Respiratory Syncytial Virus Bronchiolitis in an Infant: A Case Report
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Citation

Abstract
A Hispanic female presented to a primary care physician with copious nasal discharge and congestion at 5 days of age. The physician recommended irrigation with nasal saline and bulb suctioning at home. The infant's condition deteriorated and she was taken to the emergency department 3 days later. A nasal washing testing for respiratory syncytial virus was positive. She was hospitalized and initially treated, but the respiratory distress worsened. The infant was transferred to the Pediatric Intensive Care Unit where chest x-rays confirmed bronchiolitis. Showing no improvement with albuterol nebulization, she was by day 10 of life, intubated and put on mechanical ventilation. The case history illustrates the need for further research on risk factors contributing to severe respiratory illness in infants and, for further research on the treatment of respiratory syncytial virus bronchiolitis in hospitalized infants.

INTRODUCTION
Bronchiolitis, the leading cause of infant hospitalization in the United States (US), is a disorder of the lower respiratory tract that occurs most commonly in young children, especially during the first year of life.1 Bronchiolitis is caused by infection with a contagious seasonal virus such as respiratory syncytial virus (RSV).2, 3 The respiratory disorder is characterized by acute inflammation, edema, necrosis of the epithelial cells lining the small airways, and increased mucus production.4 This process can lead to symptoms which range from mild rhinorrhea and cough to more severe symptoms such as wheezing, respiratory distress, apnea, and hypoxemia.4 Most cases commonly occur from December to March.4 In the US, 44% of infants in their first year of life will be treated for RSV bronchiolitis. Although 95% of these infants will be treated as outpatients or in emergency departments (ED), 5 hospital admissions for bronchiolitis have almost doubled over the past 10-15 years.2 Morbidity and mortality remain relatively constant.2

AMERICAN ACADEMY OF PEDIATRICS RECOMMENDATIONS
The American Academy of Pediatrics (AAP) published a treatment guideline for bronchiolitis in 2006.4 However, many clinicians believe the guideline does not reflect current practice.6 For example, although the guideline states that neither bronchodilators nor corticosteroids have been found to have significant efficacy in the treatment of bronchiolitis, some studies have emerged with differing conclusions. A study in 2004 demonstrated the efficacy of nebulized bronchodilators and systemic corticosteroids.7 In a landmark study published in 2009, Plint and colleagues found that while nebulized bronchodilators nor systemic corticosteroids given alone did not alter clinical outcome, the concurrent use of both resulted in decreased rates of hospitalization and respiratory distress.2

According to AAP, an evidence-based approach to guideline development requires that an explicit link between evidence and recommendations be defined.4 A current lack of evidence supporting traditional treatments partially explains why the current AAP guideline does not specifically address how to care for hospitalized pediatric patients with bronchiolitis and instead focuses more on what treatments are not routinely recommended (e.g., use of bronchodilators, corticosteroid medications, ribavirin, antibacterial agents, and chest physiotherapy). The specific recommendations for treatment include intravenous (IV) fluids for hydration, supplemental oxygen (O2) if saturations consistently remain below 90%, and suctioning nasal secretions.4

PATHOPHYSIOLOGY OF RSV
Human RSV is arboviral nucleic acid (RNA) virus. The virion consists of a nucleocapsid contained within a bilayer lipid envelope that originates from the host cell plasma.
membrane. The virus is transmitted primarily through direct contact of respiratory secretions with nasopharyngeal or conjunctival mucus membranes. The virus is initially replicated in the nasopharyngeal epithelium then spreads downward to the bronchiolar epithelium and causes necrosis of the bronchiolar epithelium, lymphocytic peribronchiolar infiltration, and submucosal edema. Mucus secretions become thick, are produced in large quantities, and mix with cellular debris causing mucus plugging with increased expiratory resistance, partial airway obstruction, and air trapping. Clearance of the mucus plugs is difficult for the infected individual due to the loss of ciliated epithelium and viscosity of the secretions.

The virus can live on skin and hard surfaces from 20 minutes up to 8 hours. The incubation period ranges from 2 to 8 days and average viral shedding is about 8 days. These viral characteristics highlight the importance of hand washing and contact precautions to limit the spread of RSV infection.

**RISK FACTORS FOR SEVERE DISEASE**

The AAP guideline for treatment of bronchiolitis identifies risk factors for severe disease which include age less than 12 weeks, prematurity, cardiopulmonary disease, immunodeficiency, and a history of previous wheezing. Other studies have identified additional risk factors such as O2 saturation less than 92% and respiratory rate greater than 60 breaths per minute (bpm). In addition, evidence shows that children of minority ethnicities, children with public insurance, Medicaid status, maternal age between 15 to 19 years old, positive RSV result, maternal history of asthma or smoking, exposure to environmental tobacco smoke (ETS), and increased viral load are also risk factors for severe disease. The infant in this case report presented with 5 of the risk factors for severe disease listed above. The infant was Hispanic, less than 12 weeks old, had Medicaid insurance, exposure to ETS, and a positive RSV test result.

**CASE STUDY**

An 8-day old Hispanic female infant was taken to the ED for breathing and feeding difficulties. She tested positive for RSV. The infant was hospitalized and treated with albuterol nebulization every 4 hours. Suctioning of nasal secretions was performed, as per the AAP treatment guideline. When the infant failed to respond to this therapy, she was transferred on day 9 of life to the Pediatric Intensive Care Unit (PICU). The working diagnosis was respiratory distress and subsequent respiratory failure secondary to RSV bronchiolitis. The infant was intubated and placed on mechanical ventilation.

**Chief Complaint and History of Present Illness**

The mother stated the infant has had nasal congestion since birth and had developed a cough. On day 5 of life, the primary care physician (PCP) prescribed nasal saline drops and bulb suctioning of the nasal secretions. Three days later (day 8), the infant had difficulty feeding due to excessive nasal secretions. The infant was taken late that evening to the ED of a small local general hospital. The infant tested positive for RSV on nasal swab. Because she was born full term, the infant did not meet the criteria for RSV prophylactic therapy with Synagis, which is a costly drug used for prevention of RSV in premature infants. The infant was admitted overnight to the pediatric floor for close monitoring and frequent nasal suctioning to prevent accumulation of mucus in the nasal passages. Nasal saline was used to facilitate aspiration of the secretions and to prevent trauma to the nares. She received IV fluids for hydration at a maintenance rate and albuterol 1.25 milligrams (mg) nebulizations every 4 hours. The initial O2 saturation was 98% on room air, but dropped during the first night of hospitalization on the pediatric floor. The infant required supplemental O2 via nasal cannula at 2 liters per minute (lpm) which improved O2 saturation from 88% to 96%. The infant’s respiratory distress increased by the following morning (day 9), and she was evaluated by the pediatric team consisting of a pediatric nurse practitioner and a pediatric hospitalist.

**Past Medical History**

The infant was born full-term via spontaneous vaginal delivery at 39 weeks gestation to a 21 year old Hispanic woman. Maternal labs were unremarkable: A test for human immunodeficiency virus (HIV) was negative, rapid plasma reagin (RPR) was non-reactive, group B streptococcus was negative, and the rubella result indicated immunity. Rupture of membranes was induced during the labor process. This delivery was the mother’s second child. The infant weighed 3.45 kilograms (kg) at birth and did not suffer perinatal complications. She received her first hepatitis B vaccine in the hospital’s nursery. The infant has no known drug allergies.

**Family History**

The infant lived with extended family as well as her parents, a 2 year old sibling, and a 2 year old cousin in a house where
some of the adults smoke. The mother reported that the older children were coughing and congested. Although later discovered that one child had tested positive for RSV and was at that time hospitalized, the hospital team was unaware of this history at the time of the infant’s admission. The mother reported no family history of asthma or reactive airway disease.

Review of Systems

The mother reported the following history:

Constitutional. No fussiness or fever but difficulty feeding due to nasal congestion. Infant struggles to feed and breathe at the same time.

Head, Eyes, Ears, Nose, Throat. History of nasal congestion since birth, worsened by day 5. Nasal discharge described as thin and clear with an occasional thick white mucus plug removed by bulb aspirator.

Respiratory. Productive cough and choking on phlegm day prior to admission. Mother reports the infant’s chest occasionally “moves fast and sinks in”. Gastrointestinal. No vomiting or diarrhea. Infant continues with usual voiding and stooling pattern. Continues breast feeding and bottle feeding usual 2 ounces of infant formula every 2 to 3 hours but takes approximately 20 minutes longer due to frequent breaks during each feeding.

Neurological. No seizures or changes in mental status. Active and alert, trying to sleep but with difficulty due to nasal congestion.

Integumentary. No rashes or skin breakdown.

Musculoskeletal. No joint edema or decreased range of motion.

Focused Physical Exam

A physical exam conducted in the pediatric inpatient unit gave the following values: weight 4.3kg, temperature 99.9°F, pulse 140 beats per minute, respiratory rate from 32-60 bpm, and blood pressure of 77/61. Oxygen saturation was 96% on 2 lpm of O2 per nasal cannula. The infant was awake and alert with good muscle tone and moving all extremities. The head was atraumatic and normocephalic with a soft and flat anterior fontanelle. Mucous membranes were moist. Skin turgor was adequate. Pupils were equally round and reactive to light without redness or drainage. Tympanic membranes were within normal limits. The infant had copious clear nasal secretions and developed nasal flaring after 8 hours on the pediatric floor in spite of frequent nasal suctioning and respiratory therapy. The neck had full range of motion with no meningealismus or lymphadenopathy. The chest had mild bilateral subcostal retractions with diffuse expiratory wheezing and referred upper airway noise. Adequate air exchange was present initially with only a mild occasional productive cough present. The heart had a regular rate and rhythm. All other system aspects of the infant appeared unremarkable and were non-contributory to diagnosis and treatment.

Laboratory Data

Initial data obtained in the ED included an RSV antigen test, which was positive, and influenza A and B antigen tests, which were negative. Chest x-ray (CXR) and blood work were not initially obtained.

Differential Diagnoses

Differential diagnoses for the 9-day old infant included the following:

Impending respiratory failure
Pneumonia
Respiratory distress and hypoxemia secondary to acute RSV bronchiolitis.

Diagnostics

Due to the infant’s deteriorating respiratory status during the first hours on the pediatric ward, albuterol nebulization frequency was increased to every 3 hours. When no significant improvement was shown after 4 hours, the infant was given an IV dose of dexamethasone and a racemic epienehrine nebulization. The clinical team used traditional interventions even though the evidence was sparse to support the treatment. The chosen treatments provided temporary improvement of the symptoms as evidenced by a decrease in retractions and wheezing. The improvement lasted approximately 1 hour. Oxygen saturation continued at 96% on 2 lpm per nasal cannula, and the respiratory rate was consistently in the 50s and 60s bpm. A 2-view CXR performed at this time revealed perihilar infiltrates bilaterally with areas of peribronchial cuffing and no consolidations, an interpretation consistent with acute bronchiolitis.

Working Diagnosis

The working diagnosis was impending respiratory failure.
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and/or pneumonia secondary to RSV bronchiolitis. The infant was transferred to PICU, where the hospital team discovered her cousin, also with RSV bronchiolitis. Laboratory studies were obtained, including a complete blood count (CBC) and arterial blood gases (ABG). The CBC components included values for white blood cells (WBC), red blood cells (RBC) and mean corpuscular volume (MCV). The ABG results documented current fraction of inspired oxygen (FiO2) the infant was receiving and included pH (acidity), pCO2 (partial pressure of carbon dioxide), pO2 (partial pressure of O2) and bicarbonate (HCO3). Blood, urine, and nasopharyngeal cultures were collected as well. Imaging data presented included CXRs, ultrasound of the head, and a two dimensional echocardiogram (2D echo). Laboratory and diagnostic testing results obtained from the infant’s arrival to PICU (day 1) to post extubation (day 21) are shown in Tables 1, 2, and 3.

Table 1
Blood Gases and C-Reactive Protein

<table>
<thead>
<tr>
<th>Laboratory Tests</th>
<th>Infant 1</th>
<th>Infant 2</th>
<th>Infant 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCO3</td>
<td>28.3</td>
<td>23</td>
<td>26.6</td>
</tr>
<tr>
<td>Base Excess</td>
<td>-1.5</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td>Ca x saturation</td>
<td>100</td>
<td>56</td>
<td>81</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>less than 0.29</td>
<td>36</td>
<td>51</td>
</tr>
</tbody>
</table>

SUMMARY OF HOSPITALIZATION BY SYSTEMS
Respiratory

The infant had a significant increase in respiratory rate and decrease in O2 saturation. Although she was placed on supplemental O2 via high flow nasal cannula (HFNC), she showed no improvement. High flow nasal cannula has been demonstrated as a valuable non-invasive method of oxygenation in neonates. A series of capillary blood gases revealed worsening respiratory acidosis. Whereas an initial CXR when the infant was admitted to PICU revealed only bronchiolitis, a repeat CXR after 24 hours showed right upper lobe pneumonia with significant atelectasis of the left lower lobe. The infant was intubated and placed on mechanical ventilation. A left femoral central venous line and a right femoral arterial line were placed.
Synchronized intermittent mandatory ventilation (SIMV) was utilized with the highest settings at a rate of 40, with FiO2 65%, inspiratory time (iT) 0.5, pressure support (PS) 10, peak inspiratory pressure (PIP) 24 centimeters of water (cmH2O), and positive end expiratory pressure (PEEP) of 7cmH2O. During the time on mechanical ventilation, the infant received albuterol nebulizations every 2 hours initially and then every 3 hours. Breath sounds varied while she was on mechanical ventilation. The infant had good air movement but continued with coarse breath sounds, occasional decreased breath sounds at the bases, scattered wheezing, and prolonged expiratory sounds. The wheezing improved intermittently, particularly after nebulized albuterol treatments. She also received IV corticosteroids every 8 hours for 1 week after which she was switched to a tapered oral route.

Arterial blood gases and a CXR after 17 days of mechanical ventilation revealed marked improvement. Ventilator settings were reduced, and the infant was extubated on day 18 of mechanical ventilation. The infant transitioned to HFNC for 3 days, to regular cannula for 1 day, and then to room air. The final CXR done 2 days post extubation revealed only stable bronchiolitis.

Neurological
While intubated, the infant required sedation with fentanyl and versed; and paralysis with vecuronium. The patient did receive daily vacations from the paralytic agent. During these vacation periods she would become restless and agitated and was breathing out of synchrony with the ventilator. The paralytic agent was completely discontinued 48 hours prior to extubation. The fentanyl and versed drips were weaned 24 hours prior to extubation and methadone was initiated at that time for treatment of expected withdrawal from opioids and benzodiazepines. Upon extubation, the infant did show withdrawal symptoms such as jitteriness and trembling of the extremities. These symptoms were treated with methadone and lorazepam, from which she was gradually weaned over 6 days before discharge. Although the chosen treatment was supported by recent evidence, a current recommended option is to provide intermittent doses of sedatives and opioids during mechanical ventilation as opposed to continuous infusions.21 The electroencephalogram was normal, and an ultrasound of the head was within normal limits without evidence of intracranial bleeding or hydrocephalus.

Hematological
The infant required 1 packed red blood cell transfusion due to decreased hemoglobin and hematocrit. Tests showed appropriate increase after transfusion. The hemoglobin prior to transfusion had dropped from 15.1 grams per deciliter (gm/dL) on admission to 7.4 gm/dL. The FiO2 at this time was 45%. The hemoglobin improved to 10.6 gm/dL 24 hours post transfusion and to 14.2 gm/dL 48 hours post transfusion.

Gastrointestinal
The infant was fed via a nasoduodenal (ND) tube while on mechanical ventilation. The infant received either expressed breast milk or infant formula via ND tube at a rate of 12 milliliters (ml) per hour. She also had a nasogastric tube in place which was connected to low-intermittent wall suction. She did not experience any problems with the ND feedings.

Cardiac
On day 3 of mechanical ventilation the infant was clinically diagnosed with pulmonary hypertension (PH) due to persistent desaturations and hypotension. Pulmonary hypertension occurs when a disease elevates pulmonary arterial pressure above normal. Pulmonary disease is a common cause of pulmonary hypertension because it increases pulmonary vascular resistance (PVR), subsequently increasing pulmonary arterial pressure.22 A pediatric cardiology consult was request and a 2D echocardiogram was performed. The echocardiogram revealed a small PFO with left to right shunting, mild bilateral pulmonary arterial branch stenosis, and mild tricuspid regurgitation. Although the echocardiogram was not severely abnormal and an electrocardiogram (ECG) demonstrated a sinus rhythm, the pediatric cardiologist agreed with the clinical diagnosis of pulmonary hypertension. Treatment of PH is aimed maintaining systemic resistance while selectively lowering PVR.22 In this infant, systemic vascular resistance was maintained with IV fluids, dopamine drip for inotropic support, and milrinone drip for its pulmonary vasodilator properties and cardiotropic effects.23 Milrinone is a selective inhibitor of phosphodiesterase III and cardiac smooth muscle which has been shown to reduce PVR and pulmonary artery pressure.23 The dopamine drip was titrated to keep blood pressures in the mid 70s-80s mmHg range. The highest dopamine dose required was 10 micrograms per kilogram per minute (mcg/kg/min) and was able to be weaned off completely after 8 days. PVR was lowered by initially having high O2 concentrations up to 65% FiO2. However when the
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Infant persisted with refractory hypoxemia, inhaled nitric oxide (iNO) was administered. Inhaled iNO causes vascular smooth muscle relaxation which results in vasodilatation and subsequent decrease in PVR with improvement in oxygenation. The vasodilator effect of iNO is confined to the pulmonary system with virtually no systemic effect. Initial dose of iNO was 18 parts per million (ppm). Within 24 hours, iNO was decreased to 16ppm, then 6ppm 2 days later. On day 5 of iNO therapy the dose was 3ppm and completely off after 6 days of iNO therapy.

Infectious disease

Blood and urine cultures were done upon admission to the PICU. On the second day in the PICU the infant became febrile and was found to have pneumonia. A lumbar puncture for cerebrospinal fluid (CSF) culture was performed at that point and the infant was placed on IV ampicillin and cefotaxime. Ampicillin is a broad spectrum antibiotic recommended as initial treatment in neonates with suspected sepsis. The antibiotic covers streptococci, pneumococci, enterococci, non-penicillinase-producing staphylococci, Listeria, meningococci and some strains of Haemophilus influenzae, Proteus mirabilis, Salmonella, Shigella, Escherichia coli, Enterobacter and Klebsiella. Combination therapy of ampicillin with an aminoglycoside, such as gentamicin, is generally used as initial therapy.

However, in the case of this infant, a third generation cephalosporin (cefotaxime) was chosen as the adjunctive antimicrobial due to concerns of meningitis and the local prevalence of gram-negative organisms. Third generation cephalosporins are a reasonable alternative and provide excellent penetration of CSF as reported in a clinical report from AAP. On the third PICU day, due to persistent respiratory problems, the infant was tested for mycoplasma and pertussis. Azithromycin was added to the treatment to cover mycoplasma and pertussis. The infant had completed a 5-day course of azithromycin when test results for mycoplasma and pertussis were reported as negative. Due to the addition of a third antibiotic, she was prophylactically placed on IV fluconazole for the prevention of an opportunistic fungal infection. The ampicillin was discontinued after blood, urine, and CSF cultures were negative for 72 hours, and fluconazole was discontinued at that time as well. Cefotaxime was continued at 50mg/kg/dose every 8 hours for 10 days for treatment of right upper lobe pneumonia. Cefotaxime was discontinued when results of a tracheal aspirate culture were positive for enterobacter even after several days of cefotaxime. The decision was made at that time to switch antibiotic treatment to cefepime, a fourth generation cephalosporin. The infant received cefepime for a total of 8 days. A pediatric infectious disease specialist was involved in the care management.

CONTINUITY OF CARE

After 23 days in the hospital, the infant was transferred back to a regular pediatric floor. After 25 days in the hospital, the infant was dismissed home in stable condition. She had been off O2 for 24 hours and was off of other medications except for albuterol nebulization every 4 hours. The parents attended a cardio-pulmonary resuscitation (CPR) class while the infant was hospitalized, and were counseled on the danger of second-hand smoke. A smoking cessation brochure was provided to the parents at the time of discharge. The parents were encouraged to obtain influenza immunizations for themselves and other household members older than 6 months of age. Discharge medications were albuterol nebulization every 4 hours and Pulmicort nebulization every 12 hours. The parents were instructed to take the infant for a follow-up appointment with the PCP in 48 hours (or sooner if concerns arose). The parents were told to monitor the infant’s developmental milestones carefully. Possible effects of prolonged mechanical ventilation compounded by pulmonary hypertension at such a young age, such as developmental delay or hearing and vision problems, were discussed at length. In accordance with a recent study, long term respiratory consequences of RSV infection were discussed that included a propensity for reactive airway disease or chronic lung disease. The parents were also given follow-up appointments with a pediatric cardiologist to follow-up on the PFO and PH, a pediatric neurologist to closely monitor for any signs of developmental delay, and a pediatric pulmonologist due to high probability of chronic lung disease.

CONCLUSION

Current evidence supports that specific risk factors are associated with severe bronchiolitis and the need for hospitalization. Some of these risk factors are well recognized by AAP such as age less than 12 weeks, prematurity, cardiopulmonary disease, immunodeficiency and a history of previous wheezing. Other risk factors including minority ethnicity (e.g., Hispanic), 10,11 children with public insurance, Medicaid status, maternal age between 15 to 19 years old, positive RSV result, 14,15,5 maternal history of asthma or smoking, exposure to environmental tobacco smoke, and increased viral load.
are emerging in the literature and worthy of consideration. The case report of the otherwise healthy newborn with RSV bronchiolitis presented here illustrates the potential impact of risk factors for severe disease.

Currently, the AAP guideline does not specifically address management of a hospitalized patient with bronchiolitis, such as the concurrent nebulized bronchodilator therapy and IV corticosteroids which this infant received during the period of mechanical ventilation in the PICU. However, evidence is emerging that supports the use of treatment offered to this infant including studies by Kuyucu et al. as well as Flint and colleagues.2,7 Although not administered to this infant, hypertonic saline nebulizations have been found to decrease length of stay in a 2008 Cochrane Review by Zhang et al.27

In the case of the newborn Hispanic infant, the PCP was not aware of the infant’s close contact with an RSV positive child. Perhaps if the PCP had known this history, the provider would have tested the infant for RSV and had the mother bring the infant back for a follow-up appointment the next day. Whether or not knowing the infant’s RSV status at 5 days of life would have made a difference in avoiding mechanical ventilation is difficult to determine. The infant had multiple additional risk factors for severe disease as previously mentioned. However, practitioners should be encouraged to test for RSV in very young symptomatic infants or children since research has shown that severity of the disease and need for hospitalization may be predicted with positive RSV results.5,14,15

Evidence-based practice guidelines for the treatment of hospitalized infants with bronchiolitis need to be updated to incorporate more recently identified risk factors and related treatments reported in the current literature. Barber and colleagues noted that evidence-based guidelines can alter clinical practice.28 Clinicians should be familiar with risk factors for severe RSV disease and with potential complications during treatment such as those presented in this case study. Risk factors should be carefully assessed when determining the best course of action, and clinicians should be prepared to treat complications such as respiratory failure, secondary bacterial infections, pulmonary hypertension, anemia, reactive airway disease, or chronic lung disease.

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