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Case report

Pneumococcal septic shock after neonatal respiratory syncytial virus bronchiolitis: A case report and literature review

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Abstract. *Background***:** Bronchiolitis is a common cause of hospitalisation of infants less than a year old, with most infants recovering without complications. Respiratory syncytial virus (RSV) is a leading cause of bronchiolitis. Antimicrobial stewardship programmes do not recommend antibiotics for viral infections in neonates unless documented evidence of secondary bacterial infection is present. *Case report:* We present the case of a 7-day-old infant admitted to hospital with chest retractions and fever. The baby was hospitalised, empirical antibiotic therapy was administered, and non-invasive ventilation was started. When the viral aetiology was identified and clinical conditions improved, antibiotics were discontinued. However, after 48 hours, the newborn's condition worsened because of pneumococcal septic shock. Intravenous fluids, catecholamine support, and wide-spectrum antibiotics were administered. Non-invasive ventilation was re-started and continued until the full recovery. *Conclusions:* There is increasing evidence that RSV and *S. pneumoniae* co-infect and interact with each other, thus increasing respiratory diseases' severity. We provide a brief overview of the main international guidelines for managing bronchiolitis. Guidelines suggest avoidance of antibiotics use when the diagnosis of viral bronchiolitis is confirmed. We discuss the uncertainties regarding antibiotic use, especially in younger infants, who are more exposed to risks of bacterial superinfection. (www.actabiomedica.it)

Key words: Respiratory syncytial virus, Bronchiolitis, *Streptococcus pneumoniae*, Newborn, Antibiotic therapy, Case report

Abbreviations

CO2: Carbon dioxide; CPAP: Continuous positive airway pressure; CSF: Cerebral spinal fluid; DOL: Days of life; NICU: Neonatal intensive care unit; RSV: Respiratory syncytial virus; WBC: White blood cell

Introduction

Bronchiolitis is the most frequent lower respiratory tract infection and a common cause of hospitalisation of infants less than a year old. Respiratory syncytial virus (RSV) is its most common causative agent (1). Predominantly, most children with bronchiolitis recover without any problems; however, some children may develop complications, especially those with a history of preterm

delivery, immunodeficiency, younger age, or underlying cardiopulmonary disease (2). Although a rare occurrence, bacteria and viruses may co-infect. They can have synergistic effects and lead to severe co-infections, particularly in newborns and infants. (1-3). *Streptococcus pneumoniae* is an unfrequent causative agent of neonatal sepsis and meningitis (2.6%) (4). S. *pneumoniae* infection's mortality rate is high in infants less than two months old (5, 6). RSV and other respiratory viruses, such as parainfluenza, influenza, and metapneumovirus, may cause pneumonia in children indirectly by increasing their susceptibility to invasive bacterial diseases. Retrospective studies have shown that a relatively small percentage (1–3%) of RSV bronchiolitis cases is complicated by bacterial superinfection; however, a significant fraction (11%) of the hospitalised infants with a severe illness require intravenous antibiotics to treat serious pneumococcal disease. Furthermore, there is increasing evidence that RSV and *S. pneumoniae* co-infect and interact, thus, increasing respiratory disease severity in animal and human models (7, 8). Mechanisms underlying bacterial superinfections include virus-induced local destruction of the epithelium, compromising the host's physiologic barrier, and virus-induced modulation of the immune response. In addition, enhanced bacterial adherence to virus-infected cells is emerging as an important factor in increasing the risk of bacterial superinfections (9, 10). Generally, antibiotics should not be administered unless there is evidence of coexisting bacterial infection (3, 11). However, RSV infections tend to be dynamic, making it difficult to predict complications or bacterial co-infections, especially in children less than 12 months old (11).

We present a case of a 7-day-old infant with RSV bronchiolitis, who subsequently developed septic shock due to *S. pneumoniae* serotype 3 co-infection. Additionally, we reviewed the literature for acute bronchiolitis treatments and discussed the uncertainties of antibiotics use as part of neonatal bronchiolitis treatment.

Case Report

A male neonate was born at 37 weeks of gestation through caesarean section due to a breech presentation. Apgar scores were 8 and 9 at the 1st and 5th minutes, respectively. The baby was admitted to neonatal intensive care unit (NICU) at seven days of life (DOL) because of chest retractions and fever (38.5°C). At admission, he was pale with moderate tachypnoea and dyspnoea and chest auscultation revealed bilateral fine gasps. Chest X-ray showed accentuated bronchovascular markings. White blood cell (WBC) count was 11.9 × 10^9/L (polymorphonuclear cells, 59.4%), the C-reactive protein level was within a normal range, and the blood culture was sterile. RSV type A was identified from the nasal secretion sample using multiplex polymerase chain reaction. The nasopharyngeal samples were negative for bacteria. Empirical antibiotic therapy (penicillin 150.000 IU//kg/die and gentamicin 5 mg/kg/die) was administered after admission to the NICU. Nasal continuous positive airway pressure (nCPAP) was started a few hours after admission, and an increasing fraction of oxygen was required because of the worsened respiratory conditions. In the following hours, *i.v.* systemic corticosteroids were added to the therapy. Chest X-ray scan, after 24 hours of admission, showed opacities in the upper right and hilar-perihilar left lung regions (Fig. 1/A). Antibiotics were discontinued after four days of therapy because of the infant's clinical improvement, the sterile blood culture, the RSV detection in the nasopharyngeal samples, and the normal procalcitonin levels; nCPAP was replaced with high-flow nasal cannula. Three days after discontinuing the antibiotic therapy, the clinical conditions of the baby worsened. He presented with severe hypotension; *i.v.* fluids and catecholamine support were administered to treat the ongoing septic shock. Chest X-ray displayed massive opacification of the right upper and left lower lobes of the lungs (Fig. 1/B). Heart ultrasound revealed a moderately hypertrophic interventricular septum that normalised in a few days. Wide-spectrum antibiotics (ampicillin 150 mg/kg/die, gentamicin 5 mg/kg/die, and cefotaxime 100 mg/kg/die) were administered, and nasal-CPAP was re-started. The WBC count was 23.2 × 10^9/L (polymorphonuclear cells, 77.7%), and the C-reactive protein level increased to 15.2 mg/dL. Blood culture yielded *S. pneumoniae* serotype 3, whereas CSF culture was sterile; *i.v.* cefotaxime was administered for 10 days, until the baby fully recovered, and the C-reactive protein and procalcitonin levels were within normal ranges. nCPAP was discontinued after 13 days, and then, the baby was discharged

home. The following clinical course was uneventful and the neurodevelopmental outcome was within the normal range at 18 months of age.

Discussion

Globally, RSV is estimated to be responsible for approximately 34 million acute lower respiratory tract infections and up to 200 thousand deaths each year in children less than five years of age (12). The symptoms are usually mild or moderate. However, bronchiolitis can cause severe illness that requires hospitalisation, especially in children younger than three months old or with pre-existing risk factors such as prematurity or congenital heart diseases. Only a few case studies reported neonatal infections with *S. pneumoniae*, and the actual incidence of pneumococcal sepsis after RSV bronchiolitis in this age group is poorly defined. However, *S. pneumoniae* co-infection leads to severe complications such as sepsis, pneumonia, and meningitis. Additionally, the mortality rate of *S. pneumoniae* infection increases to 14% in infants less than two months old, particularly ≤ 7 days old (5, 6, 13-15).

In mice, the primary RSV infection increases the risk for a secondary pneumococcal infection through two mechanisms: decreasing bacterial clearance from the lung and increasing bacterial virulence. The exact molecular mechanisms are not fully understood. However, *in vitro* and *in vivo* studies demonstrate that RSV enhances the adherence of *S. pneumoniae* to human epithelial cells, and the co-infection of respiratory epithelium by RSV and the pneumococcus increases the number of inflammatory cells and lung inflammation (16, 17). *S. pneumoniae* has been shown to adhere to host surface molecules upregulated during RSV infection and directly to the RSV surface glycoprotein G present on the infected host cell membrane. Although the theory that respiratory bacteria derive benefits from respiratory viral infections is well accepted, increasing evidence indicates that the converse may be true with the presence of certain bacteria modulating viral infections (12). Furthermore, specific *S. pneumoniae* serotypes (9, 14, 18, 19, and 23) are associated with more severe disease forms (8). Smith *et al*. demonstrated that RSV could directly bind to pneumococcal surface proteins and increase the pneumococcal virulence gene expression. This, in turn, would increase the bacterial adherence and infection of the human ciliated respiratory epithelium (16). *S. pneumoniae* was more frequently detected with RSV type A than with RSV type B, which may be a result of preferential adhesion to the glycoprotein of RSV type A (12).

In the current case, pneumococcal septic shock occurred after discontinuing antibiotics because of clinical improvement. The use of antibiotics in chil-

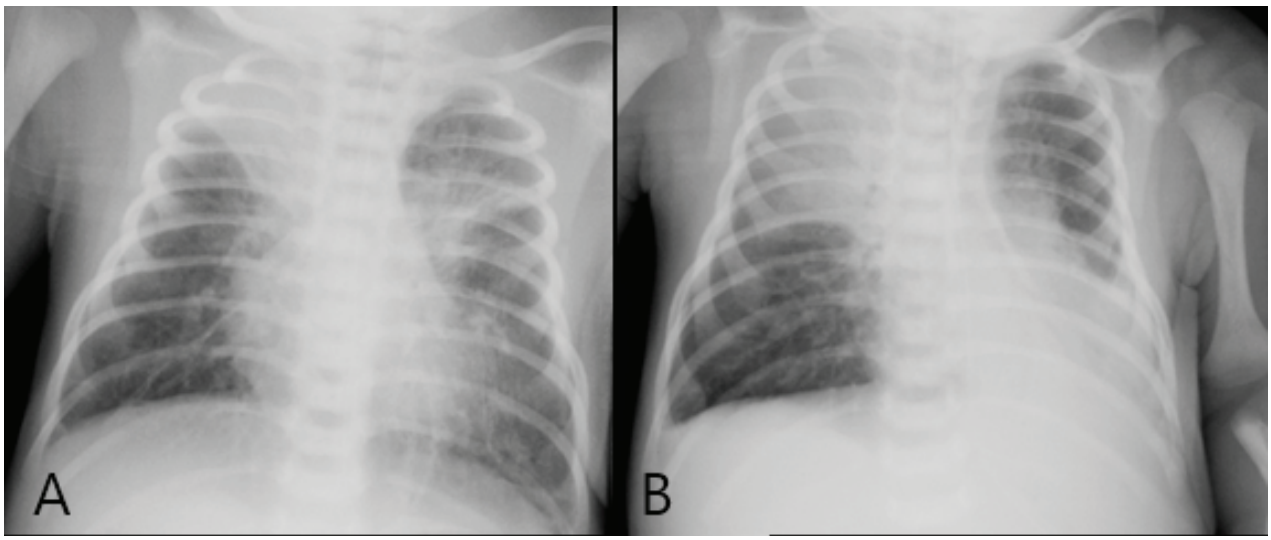

Figure 1. Chest X-ray of the newborn. A) Twenty-four hours after admission: opacities of the upper right and ilo-perilar left lung B) Seven days after admission: massive opacification of the right lung ad of lower left lung. i.v.

dren with bronchiolitis is controversial. Guidelines in the United States of America state that antibacterial medications should not be administer to infants and children diagnosed with bronchiolitis unless there is a concomitant bacterial infection or a strong suspicion (2). This is also suggested in an Italian inter-society consensus document for treating and preventing bronchiolitis in newborns and infants (2). Antimicrobial stewardship programmes recommend discontinuing antibiotics upon confirmation of viral infection and the absence of bacterial infection. However, this recommendation is often disregarded in clinical practice. Antibiotics are administered more commonly than expected (95% of the patients receiving mechanical ventilation and 34–99% of the non-ventilated children) (2, 18–21) because of fear of serious complications, such as pneumonia, septicaemia, and death (22). Approximately 21–26% of the children admitted to intensive care units with RSV bronchiolitis present bacterial co-infections or complications (19, 22). A pre-existing *S. pneumoniae* colonisation, especially in younger infants, should perhaps be considered with suspicion (17). A recent Cochrane review did not find sufficient evidence to support the use of antibiotics for bronchiolitis in children less than two years old. However, further research is needed to identify a subgroup of patients who may benefit from antibiotic treatment (22). This subgroup would include infants in the first weeks of life, and recent studies reported a higher risk of major medical interventions at this age during RSV bronchiolitis (23, 24). Pruikkonen *et al*. analysed the data of 353 infants less than six months of age, 70% of whom were admitted to the hospital for bronchiolitis; 19% required supplementary oxygen, *i.v.* fluids, antibiotics, or admission to the intensive care unit. The authors identified three signs of poor outcome: a positive RSV test result, fever above 38° C, and a low initial oxygen saturation value (24). Furthermore, the collection of samples for culture tests in bronchiolitis was controversial, as some guidelines do not mention any routine collection (25–27). In contrast, the French guidelines recommend the routine collection in infants aged less than one month (as part of full septic workup), but not for infants aged 1–3 months, unless they present with signs of severe sepsis (28).

Conclusion

This case report highlights the uncertainties in the management of viral bronchiolitis in younger infants, who have a particularly high risk of severe complications. Current uncertainties concern the decision to not initiate or to discontinue antibiotic therapies after confirmation of RSV when a young infant displays clinical improvement.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Written informed consent was obtained from the patient's parents for the publication of this case report and accompanying images.

Availability of data and materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: AB, EC, PZ, EV, and ADC made substantial contributions to the conception and design, analysis, and data interpretation. ADC, EV, EC, and PZ reviewed the literature and drafted the manuscript. AB is the corresponding author. All authors read and approved the final manuscript.

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