Group B *Streptococcus* Meningitis in an Infant with Respiratory Syncytial Virus Detection

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We report our experience caring for an infant with respiratory syncytial virus infection (RSV) and group B *Streptococcus* (GBS) bacteremia and meningitis. Concurrent GBS meningitis and RSV is rare but highlights the importance of correlating clinical symptoms with viral diagnostic testing during the evaluation of infants at risk for serious bacterial infection. *(J Pediatr 2020;225:259-62).*

Group B *Streptococcus* (GBS) infection is the most common culture-confirmed neonatal bacterial infection in the US.[1] Rates of early-onset GBS infection have declined with the implementation of maternal intrapartum antibiotic prophylaxis; however, the incidence of late-onset disease, including meningitis, has remained largely unchanged.[2-4]

Multiple studies have examined the frequency of bacterial meningitis in the setting of respiratory viral infections.[5] Three studies have evaluated the frequency of respiratory syncytial virus (RSV) associated with bacterial meningitis in febrile infants and found no cases.[6-8] Two other studies evaluated the frequency of multiple viral respiratory tract infections with bacterial meningitis in febrile infants and found no cases.[9,10]

Concurrent serious bacterial infections with respiratory viruses are considered uncommon.[5] In general, febrile infants with laboratory-confirmed viral infections appear to be at lower risk for serious bacterial infection compared with those without viral infection.[9] Of note, RSV has been associated with urinary tract infections,[5,8] and a meta-analysis[6] found similar rates of serious bacterial infection in febrile neonates aged <28 days with or without RSV detection. Given the overall low frequency of serious bacterial infection in the setting of respiratory virus infection, some have proposed that a complete sepsis evaluation might not be necessary in the setting of RSV detection for well-appearing neonates and young infants.[5,8] Moreover, Baker et al suggested that a large number of febrile 1- to 2-month-old infants can be cared for safely on an outpatient basis with strict screening criteria, which would help avoid the significant costs and risks of hospitalization.[11,12]

Many of these studies were performed when rapid antigen detection testing was the most common diagnostic assay available for viruses such as influenza and RSV. Now, with the increasing availability of more sensitive nucleic acid amplification testing, including polymerase chain reaction (PCR)-based assays, the frequency of detection of viral pathogens and serious bacterial infection may be higher than originally reported.[10] This case seeks to highlight the challenge of diagnosing serious bacterial infection in neonates, particularly among those in whom viral testing is positive. Although case reports are exempt from Institutional Review Board review, we requested and obtained consent from the patient's mother to publish the details of this case.

Case Description

A 34-day-old, previously healthy full-term female infant presented to a local emergency department (ED) with a 1-day history of fever and cough at the end of the local RSV season in May. Her mother reported decreased feeding, difficulty arousing her from sleep, and fussiness. The infant had no vomiting or change in stool pattern. There were no known sick contacts. At the local ED, she was febrile (100.6 °F), and a limited sepsis evaluation was performed. Her white blood cell count was 4900 cells/μL (68% neutrophils, with an absolute neutrophil count 3360/μL, and 25% lymphocytes), hemoglobin was 9.4 g/dL, and platelet count was 441 000 cells/μL. Urinalysis was normal, and a nonsterile, bagged urine sample was obtained. A basic electrolyte panel was normal, blood cultures were obtained, and respiratory viral testing was performed. When rapid antigen testing (Alere, https://www.globalpointofcare.abbott/en/product-details/id-now.html) revealed the presence of RSV by, the family was discharged home with reassurance.

The next day, the patient's symptoms worsened; she became progressively difficult to arouse and her parents

CSF	Cerebrospinal fluid
ED	Emergency department
GBS	Group B *Streptococcus*
PCR	Polymerase chain reaction
RSV	Respiratory syncytial virus

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The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2020.06.002

reported moaning. Her blood culture came back positive for gram-positive cocci in chains, and the family was asked to return her to the local ED. In the ED, a sepsis evaluation revealed a white blood cell count of 11 000 cells/μL (58% neutrophils, 29% lymphocytes), hemoglobin of 11 g/dL, and a platelet count of 455 000 cells/μL. Cerebrospinal fluid (CSF) was obtained, but the results were largely uninterpretable because of a traumatic lumbar puncture (protein, 108 mg/dL; glucose, 47 mg/dL; nucleated cells, 5 cells/high-power field; red blood cells, 12 990 cells/high-power field). CSF Gram stain was negative, and CSF cultures and a meningoencephalitis PCR panel were obtained. A dose of ceftriaxone was administered, and she was transferred to our facility for further evaluation and care.

On arrival to our hospital, the patient appeared clinically ill and irritable. Vital signs included temperature 100.6 °F, blood pressure 78/67 mmHg, heart rate 195 bpm, respiratory rate 40/minute, and oxygen saturation 93% in ambient air. She was tachypneic but had no abnormal findings on auscultation, and no rhinorrhea or congestion. Because of clinical suspicion of meningitis, vancomycin and ceftriaxone were started. Subsequently, blood cultures, CSF culture, and meningoencephalitis PCR panel returned positive for GBS.

Once GBS was confirmed, ampicillin monotherapy was initiated; however, the patient remained febrile for 4 days, and repeat CSF studies were obtained by interventional radiology. CSF results on day 4 of illness were consistent with meningitis and included elevated protein (171 mg/dL), hypoglycorrachia (CSF glucose 30 mg/dL, serum glucose 76 mg/dL [near the time of lumbar puncture]), elevated red blood cell count (394 red blood cells/μL), and mild pleocytosis (99 nucleated cells/μL with 22% neutrophils and 78% mononuclear cells). Gram stain of the CSF was negative, and gentamicin was administered for 48 hours until CSF cultures were confirmed to be negative.

Fever resolved on day 6 of therapy, and magnetic resonance imaging of the brain on day 12 confirmed no intracranial findings concerning for infection. A hearing screen was normal. Although unorthodox, a repeat lumbar puncture at the end of the 14-day antibiotic course was not performed, given the lack of ventriculitis on brain imaging and recent CSF studies confirming protein <200 mg/dL and neutrophil percentage <40%. The patient was discharged home with audiology follow-up and early intervention services. The family reported no neurologic complications at 1 year of age.

Discussion

GBS meningitis in the setting of RSV detection in a neonate is rare. The case illustrates the high level of suspicion that clinicians must have for severe bacterial infection in neonates, regardless of results from viral respiratory pathogen testing. Moreover, it reiterates the need for ongoing investigation of the utility of viral respiratory pathogen testing, given the increased sensitivity of molecular diagnostics and the potential for molecular diagnostic results to supplant published algorithms and clinical judgment.

The available data suggest that serious bacterial infection is more frequent in infants with no evidence of viral illness; it should be kept in mind, however, that the detection of a viral pathogen, particularly in the age of highly sensitive molecular-based assays,[10] is insufficient to conclude the presence of isolated viral disease. In our patient, although fever and cough could be reasonably attributed to RSV infection, persistent fussiness and decreased arousal should prompt consideration for serious bacterial infection. Moreover, the presence of RSV detected by rapid antigen detection testing may have provided a false sense of security in a child with features that became increasingly concerning for GBS meningitis. The Alere RSV assay is considered reliable, with reported sensitivity >98% and specificity >96% in children aged <6 months[13]; however, this test should be used when the pretest probability of RSV disease is high. Unfortunately, it can be difficult to discern whether nonspecific symptoms are attributable to RSV in neonates and young infants, such as our patient. RSV acquisition may lead to asymptomatic infection, mild to severe upper and lower respiratory tract symptoms, and nonspecific symptoms such as apnea, lethargy, and poor feeding.[14] Nonspecific symptoms are typically more common in neonates aged <3 weeks, and respiratory symptoms are typically present in infants aged >3 weeks.[14] It is also important to recognize that although infants aged 1-2 months are the most vulnerable to severe RSV disease,[14-16] infants at this age may have milder disease than might be expected due to the presence of RSV-specific maternal antibodies,[17-20] which rapidly wane over the first 6 months of life.[17,21,22] Given these considerations, it would be difficult for clinicians to credit nonspecific symptoms in febrile infants aged 1-2 months to RSV without careful exclusion of serious bacterial infection.

Multiple clinical criteria have been proposed that may identify neonates at relatively low risk for serious bacterial infection, such as the Philadelphia,[11] Rochester,[23] Boston,[24] and Milwaukee[25] criteria and the Clinical Prediction Rule developed by the Pediatric Emergency Care Applied Research Network.[26] These sets of published criteria introduce variations for consideration and have relatively similar accuracy, but emergency departments diverge in their use of and adherence to the criteria.[27-29]

Assuming that our patient appeared nontoxic to the outside ED providers based on the documented physical examination, the providers could have rightly reached differing conclusions about patient disposition depending on the algorithm chosen. Our patient likely would have been described as "low risk" based on the Boston, Milwaukee, and Philadelphia criteria, although she did not undergo an initial lumbar puncture, which all 3 criteria recommend. She also likely would have been considered "low risk" according to the Pediatric Emergency Care Applied Research Network criteria, although procalcitonin assays were unavailable to the providers. Our patient would have been described as "high risk" based on her low white blood cell count by the Rochester criteria, which does not require an initial lumbar puncture. The variation between guidelines adds to the complexity of clinical decision making and management.

As clinicians become comfortable with a "stepwise" evaluation of febrile infants, misclassification of risk for serious bacterial infection may increase. For instance, despite the high sensitivity of the Rochester criteria, the algorithm is known to misclassify some infants with bacteremia as low risk.[30] The performance of these criteria may be altered further through the use of viral respiratory pathogen testing. Rather than using viral detection to exclude bacterial infection, the complex viral-bacterial interactions for some pathogens may increase the susceptibility to serious bacterial infection. This relationship is appreciated for classic associations, such as influenza and pneumococcal disease,[31,32] but may be less appreciated for viruses such as RSV, which are equally adept at disrupting respiratory mucosa.[31-34] Given the possibility of viral-bacterial coinfection and the often devastating consequences of serious bacterial infections in neonates and young infants, providers should continue to exercise caution and careful clinical reasoning when interpreting the relevance of viral respiratory pathogen testing in febrile neonates and young infants. ■

Submitted for publication Mar 31, 2020; last revision received May 23, 2020; accepted Jun 1, 2020.

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