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Risk of Bacterial Infection in Previously Healthy Respiratory Syncytial Virus-Infected Young Children Admitted to the Intensive Care Unit

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Abstract

Objective—To evaluate the risk of bacterial infection and use of antibiotics in otherwise healthy children infected with respiratory syncytial virus (RSV) admitted to the intensive care unit (ICU).

Methods—Demographics, clinical information, interventions and outcomes were extracted from the charts of consecutive patients with laboratory-confirmed RSV infection at Children's Hospital, Boston from October 1990 through April 2002. Patients born at <36 weeks gestational age or with preexisting medical conditions were excluded.

Results—The median age of the 165 previously healthy infants infected with RSV was 42 days. Almost all patients received supplementary FiO_2, and 63 (38.2%) patients required mechanical ventilator support. No patients died. The median length of stay was 3 days in the ICU and 7 days in the hospital. Most patients had bacterial cultures sent: 155 (93.9%), blood cultures; 121 (73.3%), urine cultures; and 85 (51.5%) cerebrospinal fluid cultures. Only 1 blood culture was positive, and 1 potential urinary tract infection was identified in a patient with a negative urinalysis. All intubated patients and 80.4% of nonintubated patients received antibiotic therapy.

Conclusions—In otherwise healthy infants admitted to the ICU with RSV infection, bacteremia, urinary tract infection and meningitis are uncommon. Although bacterial pneumonia in this cohort may be more prevalent, overdiagnosis is common.

Keywords

respiratory syncytial virus; bronchiolitis; intensive care unit; sepsis

Respiratory syncytial virus (RSV) commonly infects the lower respiratory tract of infants and young children and is the most common pathogen causing bronchiolitis. Although ~1–2% of all children are hospitalized for viral lower respiratory infections in infancy,[1] only 5–10% of these hospitalized infants require intensive care in a specialized unit (ICU). Many infants admitted to the ICU with RSV infection have underlying conditions such as cardiac disease, immunocompromise or chronic lung disease that predispose them to a more severe clinical course.[2] Additionally the small airways of very young, otherwise healthy infants can also lead to significant respiratory compromise from RSV infection requiring mechanical ventilator support.

Very young infants are at high risk for serious sequelae of bacterial infection and a standard laboratory evaluation (white blood cell count, urinalysis, cerebrospinal fluid (CSF) analysis and blood, urine and CSF cultures) is generally considered for infants presenting with fever at younger than 28 days and in some infants at younger than 3 months of age.[3] Previous studies, however, have found that the risk of bacterial infection is extremely low in infants with respiratory illnesses who are RSV-positive,[4] in infants younger than 3 months who have bronchiolitis,[5] in neonates who are RSV-positive[6] and in children younger than 3 years who present to the emergency department (ED) with symptoms of a recognized viral syndrome[7] or bronchiolitis.[8] Recent reports have confirmed the lower risk of serious bacterial infections in young infants hospitalized with RSV disease.[9, 10] No studies, however, have focused on rates of bacterial infection in young children with RSV infection and respiratory symptoms who are admitted to the ICU.

The objective of this study was to identify the risk of bacteremia, bacterial meningitis, urinary tract infection and bacterial pneumonia in otherwise healthy infants admitted to a a single pediatric intensive care unit during a 12-year period and to describe antibiotic use and potential rationale for use in this population.

Methods

RSV was identified by enzyme-linked immunosorbent assay, direct fluorescent antibody or viral culture from samples obtained from nasal washes, nasopharyngeal swabs or endotracheal aspirates. Samples were collected by nurses using standard procedures. Briefly a sterile suction catheter connected to a sterile suction trap was used to aspirate secretions from the nasopharynx. If no secretions were aspirated on the first attempt, a small amount of sterile normal saline was put down a nostril, and aspiration was reattempted. The sample was then placed on ice and sent to the laboratory. As part of hospital-wide infection control practices, all RSV-positive test results were reviewed from October 1990 through April 2002. Medical records of all patients were screened to identify all otherwise healthy infants and children younger than 36 months of age. Patients were excluded if they had any underlying immune dysfunction, cardiac disease, chronic lung disease, craniofacial or upper airway abnormalities, hematologic or oncologic disorders, renal disease, neurologic dysfunction including any history of seizures, a history of birth before 36 weeks gestational age or a history of admission to the neonatal intensive care unit.

Demographics, clinical information, laboratory results, interventions and outcomes were extracted from the charts of consecutive patients identified as RSV-positive, otherwise healthy and admitted to the ICU. Clinical notes were searched to identify the results of cultures and tests reported as performed at outside hospitals before admission and to determine the reason for antibiotic use. The Institutional Review Board approved this study, and the need for informed consent was waived.

Clinical sputum specimens obtained for the diagnosis of pneumonia were evaluated in intubated patients only, because of difficulty in ensuring sample quality in nonintubated infants. Although recommendations for diagnosing bacterial pneumonia exist,[11,12] there are no clear criteria for diagnosing bacterial pneumonia in intubated infants and young children who have a viral lower respiratory infection with RSV. We made the assumption that those infants without evidence of bacterial pathogens on endotracheal culture and without evidence of inflammation as evidenced by polymorphonuclear neutrophil (PMN) count, would be less likely to have bacterial pneumonia. Therefore endotracheal cultures in intubated patients were categorized as probable, possible or no bacterial pneumonia based on review of the sputum culture and Gram-stained smear. Probable bacterial pneumonia was diagnosed if there were moderate or abundant PMNs on Gram-stained smear and growth of at least 1 potential bacterial pathogen in the absence of clear growth of normal flora. Possible bacterial pneumonia was diagnosed if criteria for probable bacterial pneumonia were not met and there were either: (1) few or greater PMNs on Gram-stained smear and growth of at least 1 potential bacterial pathogen with or without growth of normal flora: or (2) no PMNs and a pure culture of a pathogen. No infection was diagnosed if there were few to no PMNs on Gram-stained smear and no growth or only growth of normal flora.

Categoric values were compared by Fisher's exact test. Continuous variables were compared using Student's *t* test.

Results

Of 2223 hospitalized patients with positive RSV tests, 165 (7.4%) otherwise healthy RSV-positive infants who were admitted to the ICU were identified. The demographic characteristics of the population are listed in Table 1. Race was not reported in the charts of almost one-half of the children. No patients died before hospital discharge. Length of stay in the ICU and hospital was markedly longer in patients who were intubated.

Clinical interventions used in these 165 patients are reported in Table 2. All patients but 1 received supplementary oxygen. Treatments are stratified by intubation status. All intubated patients received antibiotics as did 80.4% of nonintubated patients. Intubated patients were more likely to receive antibiotics, blood transfusions, steroids, ribavirin, nasal continuous positive airway pressure, nebulized albuterol, intravenous terbutaline and vasopressors and oxygen. Ribavirin was used before 1993. No patients received RSV immunoglobulin or were managed by extracorporeal membrane oxygenation support. Thirteen patients (7.9%) had been hospitalized previously for a wheezing episode, and 30 (18.2%) were rehospitalized at Children's Hospital, Boston after this admission for a second wheezing episode.

Most ICU patients had bacterial cultures performed. Of the 165 patients, 155 (93.9%) had blood cultures, 121 (73.3%) had urine cultures and 85 (51.5%) had CSF cultures obtained (Table 3). All intubated patients had blood cultures obtained, and intubated patients were more likely to have urine and CSF cultures submitted for microbiologic evaluation. Of these cultures, one positive blood culture for *Streptococcus pneumoniae* was documented in an intubated patient who grew the same organism from the endotracheal aspirate culture. This patient appeared ill on presentation to the emergency room, was intubated and required dopamine to maintain blood pressure on ICU admission. One case of bacteriuria was identified in a patient with 3 negative urinalyses. This patient was treated clinically as having a urinary tract infection. The culture considered positive grew 30,000 colonies of *Escherichia coli*. This patient was also intubated and received dopamine for the first 5 hours of ICU admission. In addition, 30 cultures with growth of organisms were considered contaminants by the health care team.

Pretreatment of patients with antibiotics occurred in 27 (17.4%) of blood cultures, 36 (27.9%) of urine cultures and 39 (48.8%) of CSF cultures. The urinalyses results of patients who were pretreated with antibiotics before urine culture showed that 33 (91.7%) had ≤4 white blood cells (WBC) per high powered field, 1 had 5–10 WBC and 2 had 10–20 WBC. Examination of WBC counts in CSF in pretreated patients showed that all 28 of the intubated patients had ≤ 10 WBC per high powered field as did 7 of the nonintubated patients (89.7%). The 4 patients with bloody spinal fluid had 19, 25, 26 and 97 WBC with the total protein concentrations ≤71 g/dL and glucose values ≥57 g/dL.

Endotracheal cultures were obtained on 47 (74.6%) of the intubated patients, of whom 23 (50%) had received antibiotics before the culture. Using the classification system described in "Methods," 11 (17.5% of the intubated patients) had probable bacterial pneumonia, 13 (20.6%) had possible bacterial pneumonia and 23 (61.9%) did not have evidence of bacterial pneumonia and 16 (25.4%) did not have endotracheal cultures available for analysis.

Organisms associated with probable bacterial pneumonia at or near the time of admission included *Moraxella catarrhalis* (N = 5), *Haemophilus influenzae* type b (N = 4) and *S. pneumoniae* (N = 3).

Approximately 88% of all patients, and all intubated patients, received systemic antibiotics during their ICU stay (Table 4). Duration of antibiotic therapy varied, with 49 (29.7%) infants receiving ≤48 hours of antibiotic treatment, 46 (27.9%) receiving them for 49 hours–5 days and 50 (30.3%) receiving them for >5 days. The reasons given for antibiotic use are listed in Table 4. Some patients were prescribed antibiotics for more than one reason. Intubated patients were more likely to be treated for suspicion of bacterial pneumonia than nonintubated patients (34.9% versus 11.8%, respectively). The most commonly prescribed initial antibiotics were ampicillin (87 of 145 infants, 60%), gentamicin (always with ampicillin, in 41 infants, 28.3%) and cefotaxime (49 infants, 33.7%). Antibiotics were changed once in 57 infants (39.3%) and 2 or more times in 15 infants (10.3%).

Discussion

Our data show that bacterial infection of the blood, CSF or urine is extremely uncommon in previously healthy infants admitted to the ICU with RSV bronchiolitis. We found a rate of bacteremia of 0.6%, a rate of possible urinary tract infection of 0.6% and no cases of bacterial meningitis. Although some patients were pretreated with antibiotics before cultures were obtained, their urinalyses and CSF white blood cell counts and chemistries were not consistent with bacterial infection. Bacterial pneumonia is the only category of infection that may have a potentially higher prevalence. Although 75% of intubated children had endotracheal cultures sent and 35% received antibiotics for presumed bacterial pneumonia, only 17.5% showed evidence of probable bacterial pneumonia based on Gram-stained smear and culture. Antibiotics were rarely discontinued despite the low rate of laboratory-confirmed infections: greater than one-half of the patients in the ICU received antibiotics beyond a 48-hour “rule-out infection” period; and 30% of patients received antibiotics for >5 days.

Our results are consistent with the findings of other investigators who have shown that bacterial infection in the blood, CSF or urine in infants with RSV bronchiolitis is uncommon. In 1988, Hall et al[4] described a 1.2% risk of secondary bacterial infection in 565 children hospitalized with RSV respiratory illnesses. More recently, Liebelt et al[5] found no cases of bacteremia, urinary tract infection or meningitis in 211 infants age 90 days or younger admitted for bronchiolitis. Greenes et al[7] reported a 0.2% rate of bacteremia in 1347 children age 3–36 months presenting to the ED with symptoms of a recognized viral syndrome. Titus et al[6] performed a case-control study of infants 8 weeks of age or younger presenting with fever to the ED who were either RSV-positive (cases) or RSV-negative (controls) and found that the rate of serious bacterial infection was 1.1% in the RSV-positive group versus 12.6% in the controls. Melendez et al[13] found no cases of confirmed bacteremia or meningitis in 329 infants younger than 90 days of age presenting to the ED with clinical bronchiolitis but a 2% rate of urinary tract infection in boys. Kuppermann et al[8] performed a case-control study of febrile children younger than 2 years of age presenting to the ED with (cases) or without (controls) bronchiolitis on clinical examination. They reported no bacteremia and a 1.9% rate of urinary tract infection in 156 children with bronchiolitis. Antonow and Byington[14] evaluated the risk of serious bacterial infection in hospitalized children who had undergone a full sepsis evaluation (cultures of blood, urine and cerebrospinal fluid with initiation of parenteral antibiotics) and found a rate of 1.8% (5 of 282). Recent large prospective studies of serious bacterial infection in young infants with RSV have demonstrated rates of bacteremia of 0.92%[9] and 1.1% and 5.4%,[10] again similar to our findings in children hospitalized in the ICU. In the largest study reported, Purcell and

Fergie[15] reported a 1.6% rate of positive cultures (31% blood and 69% urine) in 2396 infants and children hospitalized with RSV lower respiratory infections. Whereas most of these studies have examined rates of antibiotic use and bacterial infection across either age groups or selected cohorts of patients, we have examined this in previously healthy but critically ill young children infected with RSV.

The frequent administration of unnecessary antibiotics in young children in the ICU is caused in part by the difficulty in differentiating lower respiratory tract disease from bacterial pneumonia and by the fact that approximately one-half of the patients admitted to the ICU are neonates where a septic workup for high fever is routinely performed. Otitis media was also listed as a reason for longer courses of antibiotics, but this accounted for antibiotic use in only a fraction of patients (12 of 165 or 7.3%). Of the 165 patients treated with antibiotics, only 39 (23.6%) had evidence of potential or real bacterial infection. If antibiotics had been stopped after 48 hours when infection was ruled out in the remainder of the patients, antibiotic overtreatment would have been prevented in 57 children or up to 34.5% of all the ICU admissions. The common use of antibiotics in the ICU population we found to be consistent with the use of other nonevidence based therapies, such as steroids (28.5%), albuterol nebulizer treatments (92.7%), Atrovent inhalational treatments (20.6%) and blood transfusions (34.5% of intubated patients).

One of the strengths of our study is that we have studied the largest reported population of previously healthy infants and toddlers admitted to the pediatric ICU with laboratory-confirmed RSV bronchiolitis. We excluded children with underlying diseases, who may be more likely to be susceptible to secondary bacterial infection because of underlying immunologic or physiologic dysfunction or prior hospitalizations. The limitations of our study are that not all patients had cultures sent, and many patients were treated with antibiotics before the cultures were obtained. In addition, the lack of clear diagnostic criteria in the literature for identifying bacterial pneumonia in patients with RSV lower respiratory infection may have resulted in over- or underdiagnosis of probable pneumonia in our cohort. Because of these limitations, it is difficult to make firm conclusions about whether current antibiotic practices should be altered.

Our study raises the question of whether rapid RSV and other respiratory viral testing should be available with turnaround time fast enough so that use of antibiotics could be avoided. Barenfanger et al[16] found that rapid reporting of RSV results led to decreased length of stay and better antibiotic stewardship. In children ill enough to be sent to the ICU, it may not be prudent to withhold antibiotics unless one was certain that the patient was RSV-positive, had symptoms consistent with bronchiolitis and had a chest radiograph that was not consistent with pneumonia. Discontinuing antibiotics after 48 hours in otherwise stable, healthy infants with known bacterial culture and viral test results should be considered. A prospective study would better evaluate the risk of discontinuing or not starting treatment with antibiotics in previously healthy neonates and infants admitted to the ICU with confirmed RSV bronchiolitis.

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Table 1

Demographics of Study Population Admitted to the ICU

	All Children (N = 165)	Not Intubated (N = 102)	Intubated (N = 63)
Sex			
Female	73 (44.2)*	46 (45.1)	27 (42.9)
Male	92 (55.8)	56 (54.9)	36 (57.1)
Age on admission (days)			
Mean ± SD	118.4 ± 184.7	130.1 ± 185.1	99.3 ± 184
Median	42	46.5	38
Interquartile range	22–98.5	20.8–176	22–63
Days in hospital			
Mean ± SD	8.6 ± 5.6	6.5 ± 3.2†	12.1 ± 6.9†
Median	7	5	10
Interquartile range	5–10	4–8	7–15
Days in ICU			
Mean ± SD	4.6 ± 4.2	2.7 ± 1.6†	7.7 ± 5.1†
Median	3	2	7
Interquartile range	2–6	2–3	4–9
Mechanical ventilation			
None	98 (59.4)	98 (96.1)†	0 (0)†
Intubation	48 (29.1)	0 (0)†	63 (100)†
Noninvasive	19 (2.4)	4 (3.9)†	15 (23.8)†

*Numbers in parentheses, percent.

†$P < 0.0001$.

Table 2
Clinical Interventions in the Previously Healthy RSV-Positive Children in the ICU Stratified by Need for Intubation and Mechanical Ventilator Support

Treatment	All (N = 165)	Not Intubated (N = 102)	Intubated (N = 63)	*P*
Antibiotics	145 (87.9)*	82 (80.4)	63 (100)	< 0.0001
Blood transfusion	27 (16.4)	5 (4.9)	22 (34.9)	< 0.0001
Steroids	47 (28.5)	21 (20.6)	26 (41.3)	0.007
Ribavirin	9 (5.5)	0 (0)	9 (14.3)	0.0001
RSV IgG	0 (0)	0 (0)	0 (0)	
Nasal CPAP	19 (11.5)	4 (3.9)	15 (23.8)	0.0002
ECMO	0 (0)	0 (0)	0 (0)	
High frequency vent	3 (1.8)	0 (0)	3 (4.8)	
Albuterol nebulizations	153 (92.7)	90 (88.2)	63 (100)	0.004
Epinephrine nebulizations	36 (21.8)	24 (23.5)	12 (19.1)	
Terbutaline	20 (12.1)	7 (6.9)	13 (20.6)	0.01
Atrovent	34 (20.6)	24 (23.5)	7 (11.1)	
Vasopressors	9 (5.5)	0 (0)	9 (14.3)	0.0001
Oxygen				
None	1 (0.6)	1 (1)	0 (0)	
First 24 h only	9 (5.5)	9 (8.8)	0 (0)	0.01
>24 h	155 (93.9)	92 (90.2)	63 (100)	0.01

*Numbers in parentheses, percent.

CPAP indicates continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation

Table 3

Culture Results

Culture Type	All (N = 165)	Not Intubated (N = 102)	Intubated (N = 63)
Blood			
Not tested	10 (6.1)*	10 (9.8)†	0 (0)†
Positive	1 (0.6)	0 (0)	1 (1.6)
Contaminant	6 (3.6)	2 (2)	4 (6.4)
Negative	148 (89.7)	90 (88.2)	58 (92.1)
Abx Preculture	27 (17.4)	13 (14.1)	14 (22.2)
Urine			
Not tested	44 (26.7)	37 (36.3)‡	7 (11.1)‡
Positive	1 (0.6)	0 (0)	1 (1.6)
Contaminant	19 (11.5)	16 (15.7)	3 (4.8)
Negative	101 (61.2)	49 (48)†	52 (82.5)†
Abx preculture	36 (27.9)	12 (18.5)‡	24 (42.9)‡
Cerebrospinal fluid			
Not tested	85 (51.5)	62 (60.8)	23 (36.5)
Positive	0 (0)	0 (0)	0 (0)
Contaminant	5 (3)	3 (2.9)	2 (3.2)
Negative	75 (45.5)	37 (36.3)	38 (60.3)
Abx preculture	39 (48.8)	11 (27.5)§	28 (70)§
Endotracheal			
Not tested			16
Probable			11
Possible			13
Negative			23
Abx preculture			23

* Numbers in parentheses, percent.

† $P < 0.05$.

‡ $P < 0.01$.

§ $P < 0.001$.

Abx indicates antibiotics. Percent reflects those patients who were cultured.

Table 4

Antibiotic Treatment and Reasons Listed for Prescribing Antibiotics*

Treatment	All	Not Intubated	Intubated
	N = 165	N = 102	N = 63
Duration			
None	20 (12.1)†	20 (19.6)‡	0 (0)‡
≤48 h	49 (29.7)	33 (32.4)	12 (19.1)
49 h–5 d	46 (27.9)	32 (31.4)	23 (36.5)
>5 d	50 (30.3)	17 (16.7)‡	28 (44.4)‡
Reason			
Otitis media	12 (7.3)	10 (9.8)	2 (3.2)
Pneumonia	34 (20.6)	12 (11.8)‡	22 (34.9)‡
UTI	1 (0.6)	0 (0)	1 (1.6)
Fever or high WBC	7 (4.2)	3 (2.9)	4 (6.4)
48-h rule-out	43 (26.1)	32 (31.4)	11 (17.5)
Rule out pertussis	1 (0.6)	1 (1)	0 (0)
Other	3 (1.8)	2 (2)	1 (1.6)
>1	11 (6.7)	4 (3.9)	5 (7.9)
Unclear	35 (21.2)	18 (17.7)	17 (27.0)
Initial antibiotic	N = 145 (88)	N = 82 (84)	N = 63 (100)
Amoxicillin/ampicillin alone	14 (9.6)	11 (13.4)	3 (4.8)
Ampicillin + other antibiotic	81 (55.9)	44 (53.7)	37 (58.7)
Cefotaxime/ceftriaxone alone	43 (29.7)	23 (28.0)	20 (31.7)
Cefotaxime + other antibiotic (not Amp)	2 (1.4)	0 (0)	2 (3.2)
Azithro, erythromycin or TMP-SMX alone	5 (3.5)	4 (4.9)	1 (1.6)
Changed antibiotic			
No change	73 (50.3)	46 (56.1)	27 (42.9)
Changed once	57 (39.3)	30 (36.5)	27 (42.9)
Changed ≥2 times	15 (10.3)	6 (7.3)	9 (14.3)

*Intubated versus not intubated:

‡ $P < 0.001$ comparing not intubated versus intubated using Fisher's exact test.

†Numbers in parentheses, percent.

UTI indicates urinary tract infection; Amp, ampicillin; Azithro, azithromypin; TMP-SMX, trimethoprin-sulfamethoxazole.