Empiric antibiotics are justified for infants with respiratory syncytial virus lower respiratory tract infection presenting with respiratory failure: A prospective study and evidence review*

Daniel Levin, MD; Melissa Tribuzio, MD; Tamara Green-Wrzesinki, MD; Bethany Ames, MD; Sarah Radwan, MD; J. Dean Jarvis, RN; Therese Vaccaro, MD; John F. Modlin, MD

Objective: **Although some studies indicate a low risk of serious bacterial infection in infants with respiratory syncytial virus (RSV), these studies focused on patients who did not progress to respiratory failure. We hypothesized the composite diagnosis of concomitant bacterial pneumonia (CBP) is common in lower risk infants with RSV who present in respiratory failure. The aim of the study was to investigate the incidence of CBP in low-risk infants mechanically ventilated for RSV respiratory failure and to compare the results with other studies searched for in MEDLINE.**

Design: **Prospective, descriptive study, and literature review. Two MEDLINE searches were done using the terms 1) respiratory syncytial virus (RSV) and pneumonia, and 2) RSV, pneumonia, and antibiotics.**

Setting: **Tertiary pediatric intensive care unit (PICU) in the Northeast United States.**

Patients: **We prospectively enrolled 23 infants admitted to our PICU with RSV infection and respiratory failure over a 27-month period.**

Interventions: **None.**

Measurements and Main Results: **All infants were intubated on arrival or soon thereafter; 22 had diagnostic tracheal aspiration performed, and 20 had blood cultures obtained shortly after admission. All had white blood cell count (WBC), temperature measured, and chest radiograph. Only one had antibiotics before culture. The length of mechanical ventilation, PICU course, and hospital stay were recorded.**

The primary outcome variable was the composite diagnosis of CBP as determined by the following criteria: 1) isolation of pathogenic bacteria from a tracheal aspirate, 2) blood culture, 3) chest radiograph, 4) temperature abnormality, and 5) peripheral white blood cell count (WBC). In our study, 7 infants met four criteria (probable pneumonia); 6 met three criteria (possible pneumonia); and 10 infants met less than three criteria. By tracheal aspirate criteria alone, 9 of 23 (39%) had probable pneumonia and 9 of 23 had possible pneumonia by previously published criteria. The mean length of mechanical ventilation for 7 infants who met four criteria was 10 ± 2.7 (SEM) days; for 6 infants who met three criteria, 10.5 ± 2.1 days; and for infants who met less than three criteria 7.4 ± 0.9 days. The mean PICU stay was 14.3 ± 3.6 days for infants who met four criteria; 14.3 ± 3.0 days for infants who met three criteria; and 9.9 ± 1.4 days for infants who met less than three criteria. The mean hospital stay was 16.3 ± 3.4 for infants who met four criteria; 18.7 ± 2.8 days for infants who met three criteria; and 24.8 ± 9.6 days for infants who met less than three criteria. These differences were not statistically significant. A MEDLINE search was performed using the terms 1) RSV and pneumonia, and 2) RSV, pneumonia, and antibiotics.

Conclusions: **While the small size of this study does not permit definitive conclusions, these data, in combination with other data from the literature, suggest that composite evidence of bacterial pneumonia in otherwise low-risk infants with RSV presenting with respiratory failure is 20% or higher and the use of empirical antibiotics for 24 to 48 hrs pending culture results may be justified and could be used until CBP is excluded. (Pediatr Crit Care Med 2010; 11:000–000)**

KEY WORDS: respiratory syncytial virus; bacterial pneumonia; respiratory failure

Respiratory syncytial virus (RSV) infection is one of the most common causes of hospitalization for children under 1 yr of age. Extensive studies of the epidemiology, clinical course, and response to treatment demonstrate a well defined viral syndrome with a low incidence of bacterial coinfection. However, many studies have focused on outpatients, excluding sicker hospitalized patients and those with significant respiratory symptoms and pneumonia who progress to respiratory failure (1–9), or have studied hospital-acquired infection (4). Many studies used bacteremia, bacteruria, or meningitis as evidence of bacterial infection (10–13). Most were retrospective (6–8, 10–14), and some may have underreported positive findings from their data (14). On the basis of these studies, the incidence of concomitant bacterial pneumonia (CBP) is believed to be low, and the use of antibiotics in the treatment of RSV bronchiolitis is generally discouraged.

However, our anecdotal experience in the pediatric critical care unit (PICU) suggested a higher-than-quoted incidence of

***See also p. xxx.**

From the departments of Pediatrics, Nursing, and Radiology, Children's Hospital at Dartmouth, Lebanon, NH; Red Rose Pediatrics, Lancaster, PA; Children's Medical Group, Rocky Hill, CT.

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For information regarding this article, E-mail: Daniel.L.Levin@Hitchcock.org

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Table 1. Studies about respiratory syncytial virus and serious concomitant bacterial infection

Author, Year (Reference)	Type (Retro or Prospective)	Method; Bacterial Diagnosis	Age of Patients	High-Risk Patients	PICU Admissions n Pts; Duration	Mech Vent n Pts; Duration	Hosp Stay Duration	Deaths n; %	Concomitant Bacterial Pneumonia
Nichol, 1967 (15)	P	Clinical; throat culture	<3 yrs, 62%	ND	ND	ND	ND	ND	31%
Korppi, 1989 (16)	P	Clinical; x-ray, serology, antigen	14/90 < 12 mos	ND	ND	ND	ND	ND	39%
Behrendt, 1998 (17)	R	Clinical; MD diagnosis	<12 mos; <3 yrs with chronic disease	CHD, CLD, genetic abnl, premature	8.5% Pts; ND	2.2%; ND	8–9 days, Europe	8; 0.5%[a]	26.4%, Europe
Juven, 2004 (21)	P	Clinical and antibody; viral culture, immunoassay, PCR	0.1 to 16.7 yrs	13/254 chronic conditions and others, premature, CHD	ND	ND	ND	0	29%
Bustamante, 2001 (22)	R/P	Autopsy; PCR, histopathology	<2 yrs	ND	ND	ND	ND	98; 100%	25%
Duttweiler, 2004 (23)	R	Tracheal culture	<5.8 yrs[b]; M 1.7 mos	ND	127, 100%; 4 days	57, 45%; 5 days	10 days	1; 1.7%[c]	43.9%[d]
Randolph, 2004 (14)	R	Tracheal culture[e]	<36 mos; M 42 days	Excluded	165, 100%; 3 days	63/165, 38%; ND	7 days	ND	23.4%[f]
Kneyber, 2005 (24)	R	Blood culture + 1/38 tracheal culture + 9/38 clinical; x-ray	<1 yr; M 1.5 ± 0.2 mos	Premature, CLD, CHD	82, 100%; 15.9 days + culture	65/82, 79%; 14.3 days + culture	ND	ND	26.3%[g,h,i]
Thorburn, 2006 (25)	P	Bronchoalveolar lavage, 149/162	M 1.6 mos	CHD, CLD, Immuno; airway abnl; NMD	165, 100%; ND	165, 100%; M 5 days	ND	12; 6.6%[k]	21.8%[j,l]
Resch, 2007 (26)	R	Blood and tracheal cultures	M 2 mos	Premature 42/464, 9.1%; 4 premature with pneumonia; CLD, CHD, CF, CDH, congenital abnl	30 of 42 premature; ND	M 13 days	ND	1; 0.2%[m]	27.8%[n,o]
Levin	P	Clinical; x-ray; tracheal culture	<12 mos; M 6.9 wks	Excluded	23 of 100%; M 12.5 +/− 7.1 days	23/23, 100%; M 9.1 +/− 5.1 days	20.4 +/− M 19.1 days	0	30%

P, prospective; R, retrospective; wks, weeks; mos, months; yr, year; yrs, years; M, mean; ND, no data presented; PICU, Pediatric Intensive Care Unit; n, number of patients included; pts, patients; mech vent, mechanical ventilation; CHD, congenital heart disease; CLD, chronic lung disease; abnl, abnormalties; PCR, polymerase chain reaction; IMMUNO, immunodeficiency; NMD, neuromuscular disease; CF, cystic fibrosis; CDH, congenital diaphragmatic hernia; CBP, concomitant bacterial pneumonia.

[a]8 deaths: 3 CHD/CLD; 5 < 3 months (2 of 5 premature); [b]30% high risk; [c]1 death (no systemic inflammatory response syndrome, no bacterial infection); [d]43.9% (25 of 57, bacterial pneumonia); 12 of 25 (50%) with bacterial pneumonia were community acquired; [e]1 positive blood culture (*streptococcus pneumoniae*); [f]tracheal cultures on 47 (74.6%) of the 63 intubated patients, and 23 of the 47 (50%) had antibiotics before culture; 11 of 63, 17.5%, probable pneumonia using a denominator of 63 mechanical ventilation patients; 11 of 47, 23.4%, using denominator of 47 who were actually cultured; 13 of 47 (27.6%) had possible pneumonia; [g]38 of 65 mechanical ventilation patients had cultures; [h]antibiotics in 95.1% of infants (100% of patients on mechanical ventilation); mean 7.8 days ± 0.38; 50% of patients on antibiotics prior to referral; [i]26.3% of patients on mechanical ventilation had positive cultures; [j]74 of 165 (45%) received antibiotics prior to intubation; [k]12 deaths; 5 of the 12 were related to respiratory syncytial virus; [l]probable plus possible = 70 of 165 (42.4%); [m]one term infant without bacterial coinfection died. Infant had multiple congenital abnormalities; [n]all 4 preterm infants with bacterial coinfection had pneumonia (4 of 17); [o]all bacterial infections.

bacterial pneumonia complicating RSV infection in infants in respiratory failure. Some earlier studies (15–21) found a frequent association between RSV and bacterial pneumonia, and a few more recent studies focusing on either sicker patients and those admitted to the PICU have emphasized this point (14, 22–26) (Table 1). This includes one postmortem study showing an incidence of bacterial pneumonia of 25% (22). Although most of these are retrospective (14, 17, 22–24, 26) or include a significant proportion of patients with preexisting comorbidities such as very low birth weight or other chronic medical conditions, they do support the concept of a high rate of CBP in these patients. Since the incidence of pulmonary bacterial coinfection in these studies, which ranges from 21.8% to 50%, is consistently well above that quoted in the studies involving noncritical care pediatric inpatients, we hypothesized that the clinical diagnosis of bacterial pneumonia is commonly made in previously healthy infants (without very low birth weight or other chronic medical conditions) admitted to the critical care unit with respiratory failure early in their course of RSV lower respiratory tract infection.

METHODS

Previously healthy infants <12 months of age were included in the study if they were admitted to the Children's Hospital at Dartmouth Pediatric Intensive Care Unit (PICU) with documented RSV lower respiratory tract infection (LRTI) requiring intubation for respiratory failure. Infants with pre-existing comorbidities, including prematurity <32 wks and chronic pulmonary or cardiovascular dis-

ease, were excluded. The inclusion of a control group of RSV infected patients who were not in respiratory failure was considered, but rejected because of the clinically unnecessary procedures (blood drawing, tracheal aspirate) which were deemed too invasive. The study was approved by the Dartmouth College Committee for the Protection of Human Subjects and consent was obtained for all patients.

The composite diagnosis was made using five criteria of 1) tracheal aspirate cultures obtained at or near the time of intubation and before the administration of antibiotics, 2) blood culture, 3) chest radiograph, 4) abnormal temperature, and 5) WBC abnormality. Tracheal aspirates were obtained by sterile suction using a mucus collector upon intubation or on admission for patients who were intubated before transport. In all cases but one, tracheal aspirates were obtained before administration of antibiotics. RSV infection was confirmed by testing the nasopharyngeal aspirate samples by a qualitative immunochromographic membrane assay (Binax Now RSV test, Binax, Inc., Portland, ME). All infants had blood drawn for complete blood counts on admission. Abnormal WBC was defined using age and sex-specific reference ranges (27). Blood cultures were drawn from 20 of 23 infants. All infants had chest radiographs performed within 24 hrs of admission, in most cases immediately after intubation. In addition to the original standard interpretations of the chest x-rays, the studies done shortly after admission or intubation were separately reviewed by a pediatric radiologist who was not aware of the purpose of the study. Pneumonia was diagnosed by the criteria of Kirks (28), which is patchy, asymmetric pulmonary opacities (airspace disease) as the characteristic finding of pneumonia.

Respiratory failure was defined as the inability to maintain gas exchange at a rate that matches the body's metabolic demands. Acute respiratory failure was defined as 1) arterial carbon dioxide pressure ($PaCO_2$) >55 mm Hg; 2) alveolar oxygen pressure or tension (Pao_2) <60 mm Hg, or arterial oxygen saturation (Sao_2) <90% (29), manifested by progressive clinical signs leading to fatigue and increased respiratory and heart rates. Abnormal temperature was defined as any temperature >38.0 degrees C measured rectally in infants <30 days of age; >38.1 degrees C in infants age 31 to 60 days of age; and >38.2 degrees C in infants age 61 days and over (30).

We adopted the tracheal aspirate criteria for diagnosis of bacterial pneumonia proposed by Randolph et al in 2004 (14). A diagnosis of *probable* pneumonia required the presence of moderate or abundant polymorphonuclear neutrophils (PMNs) and growth of at least one pathogenic bacterial species. *Possible* pneumonia was defined by the presence of 1) few or more PMNs *and* growth of at least one pathogenic bacterial species with or without normal bacterial flora, or 2) no PMNs and a pure culture of pathogen. No infection was diagnosed if there were few to no PMNs and no growth or growth of only normal flora. Duration of respiratory support, PICU stay, and hospital stay were determined on clinical grounds, regardless of the presence or absence of bacterial pneumonia. Infants who met four criteria were defined as having probable pneumonia, and infants who met three criteria were defined as having possible pneumonia. MEDLINE search was performed using the terms 1) RSV and pneumonia, and 2), RSV, pneumonia, and antibiotics.

Statistical comparisons were performed using a one-way analysis of variance (ANOVA) to analyze quantitative data, and the chi-square test to compare categorical data.

RESULTS

The first patient was enrolled on November 29, 2004, and the last patient in the study was discharged from the hospital on April 9, 2007. Of the 32 infants presenting to our unit during the study period, there were 6 infants who tested negative for RSV infection, 2 who did not require intubation and assisted ventilation, and 1 whose family refused consent, leaving 23 infants for final analysis. No infants were withdrawn during the clinical phase of the study.

The demographic characteristics of the final study cohort are shown in Table 2. The mean age of the 23 infants was 6.9 wks (including one 9-month-old infant who was an outlier). Seven were exposed to smoking in the home. All infants met the criteria for respiratory failure on admission, both clinically and on the basis of arterial blood gases, confirming the presence of hypoxemia and/or hypercapnia. Twenty-two of 23 infants had tracheal aspirates, and 21 of them were performed before the administration of antibiotics.

Eleven of the 23 infants had an abnormal temperature, 9 of 23 had an abnormal WBC, and 11 of 23 had pneumonia on chest roentgenogram (CXR), and none had a positive blood culture.

According to our predetermined definitions, 9 of 23 (39%) met tracheal aspirate criteria for probable pneumonia, and 9 of 23 (39%) met tracheal aspirate criteria for possible pneumonia (a total of 78% for the two categories). Pathogenic bacteria isolated from tracheal aspirates from infants with probable or possible pneumonia included *Haemophilus influenzae (nontypable)* (11), *Streptococcus pneumoniae* (1), *Moraxella catarrhalis* (2), and *Staphylococcus aureus* (2). One infant had both *Staphylococcus aureus* and *Moraxella catarrhalis* isolated from the same specimen. All blood cultures were negative, and therefore no patient met all five clinical criteria for CBP; 7 met four criteria (30%); 6 met three criteria (26%); 4 met two criteria (17%); 4 met one criteria (2%); and 2 met no criteria (4%) (Table 3). Seven of 23 (31%) infants had pneumonia by both probable tracheal aspirate plus chest radiograph criteria.

Seven of 7 infants with four criteria (probable pneumonia); 5 of 6 infants with three criteria (possible pneumonia), and 7 of 10 infants with less than three criteria (no pneumonia) received antibiotic therapy. The mean length of ventilation was 10 ± 2.8 (SEM) days in CBP-probable infants, 10.5 ± 2.1 days in CBP-possible infants, and 7.4 ± 0.9 days in CBP-negative infants. The mean length of PICU stay was 14.3 ± 3.8 (SEM) days in CBP-probable infants, 14.3 ± 3.0 days in the CBP-possible infants, and 9.9 ± 1.4 days in CBP-negative infants. Hospital stay was 16.3 ± 3.4 days in CBP-probable infants, 18.7 ± 2.8 days in the CBP-possible infants, and 24.7 ± 9.6 days in CBP-negative infants. None of the differences among the patient groups in length of mechanical ventilation, length of PICU stay, or length of hospital stay was statistically significant. Although the number of days of mechanical ventilation and PICU stay was longer in the probable and possible-pneumonia groups than in the no-pneumonia group, the small number

Table 2. Study population characteristics

Variable	Mean	+/− SD
Male, female	13, 10	
Weight (kg)	4.04	+/− 1.54
Age (wks)[a]	6.9	+/− 7.3
Duration of illness (days)	4.08	+/− 2.2
Exposure to smoke (yes, no)	7 yes, 16 no	
Dyspnea (yes/no)	23 yes	
Admission		
pH	7.33	+/− 0.07
Arterial carbon dioxide pressure	55.7	+/− 11.1
Alveolar oxygen pressure or tension	60.8	+/− 30.3
O_2 saturation	84.8	+/− 16.5
Fractional inspired oxygen	0.70	+/− 0.33

[a]This group includes one outlier who was 9 months old.

Table 3. Specific criteria for patients with probable and possible bacterial pneumonia

	Abnormal Temperature	Abnormal White Blood Cells	Pneumonia Chest X-Ray	Position Tracheal Aspirate
Patient number, patients with probable bacterial pneumonia[a]				
2	Yes	Yes	Yes	Probable
4	Yes	Yes	Yes	Probable
5	Yes	Yes	Yes	Probable
6	Yes	Yes	Yes	Possible
14	Yes	Yes	Yes	Probable
16	Yes	Yes	Yes	Possible
21	Yes	Yes	Yes	Possible
Patient number, patients with possible bacterial pneumonia[b]				
7	No	Yes	Yes	Probable
8	Yes	No	Yes	Probable
15	No	Yes	Yes	Possible
19	Yes	Not done	Yes	Probable
20	Yes	No	Yes	Possible
22	No	Yes	Yes	Probable

[a]Patient met four criteria; [b]patient met three criteria.

of patients precluded meaningful statistical comparison.

The MEDLINE search with the keywords "RSV" and "pneumonia" resulted in 31 references. Twenty were not used since they were studies of animals, adults, general infection, patients with chlamydia, atypical pneumonia, HIV, asthma, or guidelines and editorials concerning multiple issues. Of the 11 remaining articles, one was a duplicate, leaving ten. Of these, seven were clinical studies (three prospective, two retrospective, and two prospective and retrospective), one a basic science review, one a case report, and one a letter.

The MEDLINE search using the key words "RSV," "pneumonia," and "antibiotics" resulted in 24 references. Fifteen were not used since they were studies of animals, cerebrospinal fluid and middle ear infections, were broad general editorials on pneumonia, or were about adult patients. Of the nine remaining papers, four were duplicates of the other search. The five remaining papers were all clinical studies (four prospective and one retrospective).

All pertinent references are included in the text, and the remaining references are from these papers and the basic science literature.

DISCUSSION

This prospective study of previously healthy infants, who did not have very low birth weights or other chronic medical conditions, and who were intubated and ventilated for respiratory failure secondary to RSV bronchiolitis early in their course, suggests that the concomitant presence of the bacterial pneumonia is more common than expected based on previous studies of RSV-infected children that focused on patients who did not progress to respiratory failure. In some studies it is possible that the incidence of CBP may be underreported since 45% (25) and 50% (14, 24) of the patients investigated for presence of bacteria in the trachea received antibiotics before cultures were obtained.

In our study, the 30% incidence of probable CBP by clinical criteria (7 infants met four criteria), is substantiated by the 39% (9 of 23) who had probable pneumonia by tracheal aspirate criteria and the 30% (7 of 23) who had both probable pneumonia by tracheal aspirate and chest radiograph criteria. This is consistent with other studies of RSV-infected infants admitted to critical care units that report rates of 21.8% to 50% (14, 17, 18, 21, 23–26). We specifically excluded infants we considered to be high risk with conditions known to predispose to a more severe clinical course of RSV, including very low birth weight and/or those with chronic pulmonary or cardiovascular disease. Our study population has a relatively low mean age (6.9 wks, SD 7.3), which is consistent with the findings of previous large epidemiologic studies demonstrating that hospitalization for RSV is significantly more likely in the first months of life (31, 32). Exposure to secondary tobacco smoke at home may also be a relative risk factor for more severe RSV. Seven of 23 RSV-infected infants in our study were exposed to secondary tobacco smoke at home, a rate comparable to that found in other studies of hospitalized RSV-infected infants and children (32).

No clear, uniformly-established criteria for bacterial pneumonia exist on the basis of microbiological, radiologic, or clinical data. While previous studies about the incidence of bacterial pneumonia have looked at blood cultures as one of their primary outcomes, these are positive in less than half of infants and children, even in the face of otherwise overwhelmingly supportive evidence for bacterial pneumonia (5, 10, 34). We focused on variables routinely assessed by the clinician at the bedside, recognizing that while no single one of these is diagnostic, each is helpful as cumulative clinical evidence. This applies to the tracheal aspirate criteria as published by Randolph et al (14), which, although not prospectively validated, are nonetheless useful in making the diagnosis of pulmonary bacterial infection. Similarly, radiologic appearances secondary to either viral or bacterial respiratory disease cover a broad spectrum with significant overlap (33, 34), which in part accounts for the variations in the diagnosis and treatment of these infants (35, 36). While this limits the usefulness of chest radiographs in establishing a differential diagnosis in the individual patient, it is noteworthy that previous studies comparing cohorts of RSV-negative with RSV-positive patients, with and without bacterial superinfection on tracheal aspirate, showed a significantly higher incidence of normal chest radiographs in the virus positive/bacteria negative groups (37). Also, one study found a significant difference in WBC, C-reactive protein, and erythrocyte sedimentation rate in patients with RSV with lobar pneumonia on chest radiograph vs. those without lobar pneumonia, suggesting a bacterial coinfection. With regard to the remainder of our diagnostic variables, the mean temperature in patients with possible or probable pneumonia was significantly higher than in the group with negative tracheal aspirates. There was no significant difference in WBC counts. The overall sense remains that when infants present in respiratory failure, pneumonia is common in infants with viral disease, especially RSV (41, 42), and bacteria are frequently responsible (Table 1). In addition, even though the use of antibiotics for all children with bronchiolitis is not thought to be helpful, their use in a selected subset who may also have bacterial pneumonia may be indicated (43, 44).

This is not true for infants with community-acquired pneumonia who are not in respiratory failure, as show by a randomized controlled trial of antibiotics vs. no antibiotics in an earlier study (3). The observed high incidence of bacterial pneumonia in our population of ventilated children with RSV infection raises the interesting question of whether RSV infection predisposes to subsequent bacterial superinfection. Pathologic synergy between the influenza virus and *Streptococcus pneumoniae* (45) and other pathogenic bacterial is well described, but other respiratory viruses are also recognized to be associated with bacterial pneumonia (24, 46–51), including RSV (16, 23, 25, 52–54). Evidence at the molecular level suggests several mechanisms by which RSV might predispose to bacterial pneumonia: for one, RSV appears to have a significant impact on both the quality and quantity of surfactant protein A (SP-A) production (55–68). Not only is this likely to be one of the key mechanisms by which RSV causes its classic constellation of pulmonary symptoms, but SP-A deficiency also allows for increased susceptibility of the respiratory tract to bacterial infection. *Haemophilus influenzae* appears to have a particularly strong association with RSV, mostly by means of binding RSV glycoprotein (61, 69). Interestingly, nontypeable *Haemophilus influenzae* was the single most commonly isolated organism in our tracheal aspirates as has been noted previously (16).

The primary limitations of our study are the small number of patients, the absence of a control group, and the validity of the clinical criteria as evidence of bacterial pneumonia. The small number of patients was caused by our rigorous exclusion criteria to make certain we were not including high-risk patients with comorbidities and to particularly light RSV seasons during the study period. The lack of control group occurred because we focused on low-risk infants in respiratory failure presenting early in their course of RSV. We reasoned that these infants may be more likely to present in respiratory failure because they had CBP, and therefore the most appropriate control group was infants who were hospitalized early in their course of RSV but who were not in respiratory failure. This led to the problem of subjecting these infants to unnecessary tests. The number of infants in the study who had the diagnosis of CBP and who did not receive antibiotics was too small to use as a control group. The use of composite criteria to diagnose CBP, although not ideal, is what bedside clinicians have available. They frequently use tracheal aspirate in combination with chest radiograph, temperature abnormality, and WBC to make decisions for treatment with antibiotics.

We believe our study, in combination with the other studies presented (15–26), supports a sufficiently high incidence of CBP in infants mechanically ventilated early in their course for respiratory failure and RSV to justify the use of antibiotics until CBP is excluded when tracheal culture is negative (usually at 48 hrs after admission). For some infants who have a chest radiograph positive for pneumonia and continue to need mechanical ventilation, clinicians may choose to continue antibiotics after 48 hrs even if the tracheal aspirate culture is negative, especially in infants who received antibiotics before the culture was obtained. A large, prospective, randomized, multicenter study will be necessary to further resolve this issue and determine potential benefits of the length of mechanical ventilation and hospital stay in infants treated with antibiotics.

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REFERENCES

1. Field CM, Connolly JH, Murtagh G, et al: Antibiotic treatment of epidemic bronchiolitis—A double-blind trial. *Brit Med J* 1966; 1:83–85
2. Berman S, Duenas A, Bedoya A, et al: Acute lower respiratory tract illnesses in Cali, *Colombia:* A two-year ambulatory study. *Pediatrics* 1983; 71:210–218
3. Friis B, Anderson P, Brenoe E, et al: Antibiotic treatment of pneumonia and bronchiolitis: A prospective randomized study. *Arch Dis Child* 1994; 59:1038–1045
4. Hall CB, Powell KR, Schnabel KC, et al: Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. *J Pediatr* 1988; 113:266–271
5. Kupperman N, Bank D, Walton E, et al: Risks for bacteremia and urinary tract infections in young febrile children with bronchiolitis. *Arch Pediatr Adolesc Med* 1997; 151:1207–1214
6. Greens D, Harper M: Low risk of bacteremia in febrile children with recognizable viral syndromes. *Pediatr Infect Dis J* 1999; 18:258–261
7. Brooks AM, McBride JT, McConnochie K, et al: Predicting deterioration in previously healthy infants hospitalized with respiratory syncytial virus infection. *Pediatrics* 1999; 104:463–467
8. Guar A, Hare M, Shorr R: Provider and practice characteristics associated with antibiotic use in children with presumed viral respiratory tract infections. *Pediatrics* 2005; 115: 635–641
9. Jamjoon GA, al-Semrani AM, Board A, et al: Respiratory syncytial virus infection in young children hospitalized with respiratory illness in Riyadh. *J Trop Pediatr* 1993; 39:346–349
10. Hickey R, Bowman M, Smith G: Utility of blood cultures in pediatric patients found to have pneumonia in the emergency department. *Ann Emerg Med* 1996; 27:721–725
11. Purcell K, Fergie J: Concurrent serious bacterial infections in 2396 infants and children hospitalized with respiratory syncytial virus lower respiratory tract infections. *Arch Pediatr Adolesc Med* 2002; 156:322–324
12. Titus M, Wright S: Prevalence of serious bacterial infections in febrile infants with respiratory syncytial virus infection. *Pediatr* 2003; 112:282–284
13. Byington C, Enriquez F, Hoff C, et al: Serious bacterial infections in febrile infants 1 to 90 days old with and without viral infections. *Pediatrics* 2004; 1662–1666
14. Randolph A, Reder L, Englund J: Risk of bacterial infection in previously healthy respiratory syncytial virus-infected young children admitted to the intensive care unit. *Pediatr Inf Dis J* 2004; 23:990–994
15. Nichol K, Cherry J. Bacterial-viral interrelations in respiratory infections of children. *N Engl J Med* 1967; 277:667–672
16. Korppi M, Leinonen M, Koskela M, et al: Bacterial coinfections in children hospitalized with respiratory syncytial virus infections. *Pediatr Infect Dis J* 1989; 8:687–692
17. Behrendt C, Decker MD, Burch DJ, et al: International variation in the management of infants hospitalized with respiratory syncytial virus. *Eur J Pediatr* 1998; 157:215–220
18. Ruuskanen O, Nohynek H, Ziegler T, et al: Pneumonia in childhood: Etiology and response to antimicrobial therapy. *Eur J Clin Microbiol Infect Dis* 1992; 11:217–223
19. Cimolai N, Wensley D, Seear M, et al: Mycoplasma pneumonia as a cofactor in severe respiratory infections. *Clin Infect Dis* 1995; 21:1182–1185
20. Bremont F, Rittie JL, Juchet A, et al: Penicillin-resistant pneumococcal pneumonia (serotype p14), and coinfection with respiratory syncytial virus and Mycoplasma. *Arch Pediatr* 1998; 1:33s–36s
21. Juven T, Mertsola J, Waris M, et al: Clinical response to antibiotic therapy for community-acquired pneumonia. *Eur J Pediatr* 2004; 163:140–144
22. Bustamante-Calvillo M, Valazquez F, Cabrera-Munoz L, et al: Molecular detection of respiratory syncytial virus in postmortem lung tissue samples from Mexican children deceased with pneumonia. *Pediatr Infect Dis J* 2001; 20:495–501
23. Duttweiler L, Nadal D, Frey B: Pulmonary

and systemic bacterial co-infections in severe RSV bronchiolitis. *Arch Dis Child* 2004; 89: 1155–1157
24. Kneyber M, Blusse van Oud-Albas H, van Vliet M: Concurrent bacterial infection and prolonged mechanical ventilation in infants with respiratory syncytial virus lower respiratory tract disease. *Intensive Care Med* 2005; 31: 680–685
25. Thorburn K, Harigopal S, Reddy V, et al: High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. *Thorax* 2006; 61:611–615
26. Resch B, Gusenleitner W, Mueller W: Risk of concurrent bacterial infection in preterm infants hospitalized due to respiratory syncytial virus infection. *Acta Paediatr* 2007; 96: 495–498
27. Soldin SJ, Brugnara C, Wong EC, eds: Pediatric Reference Intervals, Fifth Edition. Washington, DC: AACC Press, 2005
28. Kirks D: Practical pediatric imaging 1998. In: Respiratory Systems, Third Edition. Baltimore MD: Lippincott Williams & Wilkins, pp 715–723
29. Anas NG: Respiratory failure, In: Levin DL, Morris FC, eds. Essentials of Pediatric Intensive Care, Second Edition. New York: Churchhill Livingston, Quality Medical Publisher, 1997: 69–82
30. Herzog LW, Boyne LJ: What is fever? Normal temperature in infants less then three months old. *Clin Pediatr* 1993; 32:142–146
31. Shay DK, Holman RC: Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA* 1999; 282:1440–1446
32. Simoes E, Carbonell-Estrany X: Impact of severe disease caused by respiratory syncytial virus in children living in developed countries. *Pediatr Infect Dis J* 2003; 22:S13–S20
33. Simpson W, Hacking PM, Court SDM, et al: The radiological findings in respiratory syncytial virus infection in children. *Pediatr Radiol* 1975; 2:155–160
34. Kabra SK, Lodha R, Broor S, et al: Etiology of acute lower respiratory tract infection. *Indian J Pediatr* 2003; 70:33–36
35. Aherne W, Bird T, Court SD: Pathological changes in virus infections of the lower respiratory tract in children. *J Clin Path* 1970; 23:7–18
36. Wang E, Law B, Boucher F, et al: Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of admission and management variation in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 1996; 129:390–395
37. Brand P, Vaessen-Verberne A: Differences in the management of bronchiolitis between hospitals in The Netherlands. *Eur J Pediatr* 2000; 159:343–347
38. Friis B, Eiken M, Hornsleth A. Chest x-ray appearances in pneumonia and bronchiololitis. Correlation to virological diagnosis and secretory bacterial findings. *Acta Paediatr Scand* 1990; 79:219–225
39. von Renesse A, Schildgen O, Klinkenberg D, et al: DMS RSV Study Group: Respiratory syncytial virus infection in children admitted to hospital by ventilated mechanically for other reasons. *J Med Virol* 2009; 81:160–166
40. Juven T, Mertosola J, Toikka P, et al: Clinical profile of serologically diagnosed pneumococcal pneumonia. *Pediatr Inf Dis J* 2001; 20:1028–1033
41. Saijo M, Ishii T, Kokubo M, et al: White blood cell count, C-reactive protein and erythrocyte sedimentation rate in respiratory syncytial virus infection of the lower respiratory tract. *Acta Paediatr Jpn* 1996; 38:596–600
42. Zollar L, Krause H, Mufson M: Microbiologic studies on young infants with lower respiratory tract disease. *Am J Dis Child* 1973; 126: 56–60
43. Randolph A, Meert K, O'Neil M, et al: The feasibility of conducting clinical trails in infants and children with acute respiratory failure. *Am Respir Crit Care Med* 2003; 167: 1334–1340
44. Spurling GKP, Foneska K, Doust J, et al: Antibiotics for bronchiolitis in children (review). Cochrane Database of Systematic Reviews 2007; 1: Art number CD005189. DOI: 10.1002/14651858. CD005189.pub2
45. Thorburn K, Van Saene H: Pulmonary bacterial co-infection in children ventilated for severe respiratory syncytial virus bronchiolitis is common. *Intensive Care Med* 2007; 33:565
46. Talbot T, Poehling K, Hartert T, et al: Seasonality of invasive pneumococcal disease: Temporal relation to documented influenza and respiratory syncytial viral circulation. *Am J Med* 2005; 118:285–291
47. Eichenwald HF, Kotsevalov O, Fasso LA: The "cloud-baby": An example of bacterial-viral interaction. *Am J Dis Child* 1960; 100:161–173
48. Mills E: Viral infections predisposing to bacterial infections. *Ann Rev Med* 1984; 35: 469–79
49. Trigo FJ, Breeze RG, Liggitt HD, et al: Interaction of bovine respiratory syncytial virus and Pasteurella haemolytica in the bovine lung. *Am J Vet Res* 1984; 45:1671–1678
50. Paisley J, Lauer B, McIntosh K, et al: Pathogens associated with acute lower respiratory tract infection in young children. *Pediatr Inf Dis* 1984; 3:14–19
51. Baptist E, Louthain L: Bacteremia in the infant with bronchiolitis. *Arch Pediatr Adolesc Med* 1999; 153:1309–1310
52. Hament JM, Kimpen JLL, Fleer A, et al: Respiratory viral infection predisposing for bacterial disease: A concise review. *FEMS Immunol Med Microbiol* 1999; 26:189–195
53. Loosli CG: Influenza and the interaction of viruses and bacteria in respiratory infections. *Medicine* 1973; 52:369–384
54. Tristam DA, Miller RW, McMillan JA, et al: Simultaneous infection with respiratory syncytial virus and other respiratory pathogens. *Am J Dis Child* 1960; 142:834–836
55. Meissner C: Selected population at increased risk from respiratory syncytial virus infections. *Pediatr Infect Dis J* 2003; 22:S40–S45
56. Baughman RP, Sternberg RI, Hull W, et al: Decreased surfactant protein-A in patients with bacterial pneumonia. *Am Rev Respir Dis* 1993; 147:653–657
57. LeVine AM, Lotze A, Stanley S, et al: Sufactant content in children with inflammatory lung disease. *Pediatr Crit Care* 1996; 24: 1062–1067
58. Dragaville PA, South M, McDougall PN, et al: Surfactant abnormalities in infants with severe viral bronchiolitis. *Arch Dis Child* 1996; 75:133–136
59. Pison U, Max M, Neuendank A, et al: Host defense capacities of pulmonary surfactant: Evidence for non-surfactant functions of the surfactant system. *Eur J Clin Invest* 1994; 24: 586–599
60. Wright JR: Immunomodulatory functions of surfactant. *Physiol Rev* 1997; 77:931–962
61. Manz-Keinke H, Plattner H, Schlepper-Shaefer J: Lung surfactant protein-A (SP-A) enhances serum-independent phagocytosis of bacteria by alveolar macrophages. *Eur J Cell Biol* 1992; 57:95–100
62. McNeely TB, Coonrad JD: Aggregation and opsonization of type A but not type B Hemophilus influenzae by surfactant protein A. *Am J Respir Cell Mol Biol* 1994; 11:114–22
63. Kahba K, Schmegner J, Keisari Y, et al: SP-A enhances phagocytosis of klebsiella by interaction with capsular prolysaccharides and alveolar macrophages. *Am J Physiol* 1997; 272: L344–L352
64. LeVine AM, Kurak KE, Wright JR, et al: Surfactant protein-A binds group B streptococcus enhancing phagocytosis and clearance from lungs of surfactant protein-A deficient mice. *Am J Respir Cell Mol Biol* 1999; 20:279–286
65. Van Iwaarden F, Welmers B, Verhoef J: Pulmonary surfactant protein A enhances the host-defense mechanism of rat alveolar macrophages. *Am J Respir Cell Mol Biol* 1990; 2:91–98
66. Weissbach S, Neuendank A, Pettersson M, et al: Surfactant protein A modulates release of reactive oxygen species from alveolar macrophages. *Am J Physiol* 1994; 267:L660–L666
67. Blau H, Riklis S, van Iwaarden J, et al: Nitric oxide production by rat alveolar macrophages can be modulated in vitro by surfactant protein A. *Am J Physiol* 1997; 272:L1198–L1204
68. McIntosh JC, Mervin-Blake S, Conner E, et al: Surfactant protein A protects growing cells and reduces TNF-alpha activity from LPS-stimulated macrophages. *Am J Physiol* 1996; 271:L310–L319
69. LeVine A, Bruno M, Huelsman K, et al: Surfactant protein A- deficient mice are susceptible to group B streptococcal infection. *J Immunol* 1997; 158:4336–4340
70. Avadhanula V, Wang Y, Portner A, et al: Nontypeable Haemophilus influenzae and Streptococcus pneumoniae bind respiratory syncytial virus glycoprotein. *J Med Microbiol* 2007; 56:1133–1137