Risk Model of Bacterial Coinfection in Children with Severe Viral Bronchiolitis

Michael C. Spaeder¹ Refik Soyer²

¹Division of Pediatric Critical Care, University of Virginia School of Medicine, Charlottesville, Virginia, United States

²Department of Decision Science, The George Washington University School of Business, Washington, District of Columbia, United States

Address for correspondence Michael C. Spaeder, MD, MS, Division of Pediatric Critical Care, University of Virginia School of Medicine, PO Box 800386, Charlottesville, VA 22908, United States (e-mail: ms7uw@hscmail.mcc.virginia.edu).

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Abstract

Background Among children with respiratory failure from viral lower respiratory tract infection (LRTI), up to 39% will develop pulmonary bacterial coinfection, yet nearly all will receive antibiotics. We sought to identify patients with viral LRTI requiring mechanical ventilation at low risk of bacterial coinfection through the use of a risk prediction model.

Methods We performed a retrospective cohort study identifying all patients admitted to the intensive care unit with laboratory-confirmed viral LRTI requiring invasive mechanical ventilation over a 2-year period and partitioned data in experimental and validation datasets. A multivariate probit regression model was constructed including variables associated with bacterial coinfection in the experimental dataset. Model was validated and recalibrated using the validation dataset. Model discrimination was assessed using receiver operating characteristic curve analysis.

Results There were 126 patients included in the analysis. Variables associated with bacterial coinfection included tracheostomy in situ, Gram-stained smear white blood cells, and bacteria. The final recalibrated model discriminating between no coinfection and coinfection had an area under the curve of 0.8696.

Conclusion Our prediction model identifies patients with viral LRTI requiring mechanical ventilation at very low risk of bacterial coinfection and has the potential to decrease antibiotic utilization without negatively impacting clinical outcome.

Keywords

- respiratory tract infection
- coinfection
- intensive care
- child
- pediatrics
- prediction

Introduction

In the United States, infectious respiratory illness is responsible for over an estimated 320,000 hospitalizations per year in children.¹ It is estimated that as many as one-quarter of children hospitalized with viral lower respiratory tract infection (LRTI) will require admission to the intensive care unit (ICU).² Among children with respiratory failure from LRTI caused by respiratory syncytial virus (RSV), between 17 and 39% will develop pulmonary bacterial coinfection, yet nearly all will receive antibiotics.^{3–5}

The initiation of antibiotics in this critically ill cohort may very well be warranted given the added morbidity for those with pulmonary bacterial coinfection; however, for the majority of hospitalized patients, the initiation and prolongation of antibiotics is unnecessary and potentially harmful.³ Overtreatment with antibiotics is associated with adverse drug reactions, predisposition to secondary infections (e.g., *Clostridium difficile*), and emergence and selection of drug-resistant organisms.⁶ The rate of adverse events in children receiving long-term parenteral antibiotics has been reported to be as high as 32%.⁷

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We hypothesized that in a large subset of patients with acute viral respiratory infection requiring mechanical ventilation, the risk of pulmonary bacterial coinfection is sufficiently low to warrant the discontinuation of antimicrobial therapy without negatively impacting clinical outcome. We sought to identify patients with viral LRTI requiring mechanical ventilation at low risk of bacterial coinfection through the use of a risk prediction model.

Materials and Methods

The institutional review board at the Children's National Medical Center reviewed and approved this study. We performed a retrospective cohort study identifying all patients admitted to the ICU, either pediatric ICU or cardiac ICU, at an urban academic free-standing children's hospital with laboratory-confirmed RSV, human metapneumovirus (hMPV), adenovirus, or human rhino/enterovirus (HRV/EV) LRTI requiring invasive mechanical ventilation between January 2010 and December 2011. Viral infection was defined as the identification of RSV, hMPV, adenovirus, or HRV/EV from a nasopharyngeal or endotracheal specimen by polymerase chain reaction testing. The Microbiology Laboratory at our institution uses the Qiagen Symphony RGQ (Venio, the Netherlands) platform of nucleic acid extraction and amplification, and a Luminex (Austin, Texas, United States) system and test reagents for the determination of assay results.

Bacterial coinfection was defined using previously published microbiological criteria from an endotracheal, thoracentesis, or bronchoalveolar lavage specimen obtained within 48 hours of collection of positive viral specimen.^{3,5} Probable bacterial coinfection was defined as the presence of moderate or many polymorphonuclear (PMN) cells on Gram-stained smear and growth of at least one potential bacterial pathogen in the absence of normal respiratory flora. Possible bacterial coinfection was defined as either (1) presence of few or greater PMN cells on Gram-stained smear and growth of at least one potential bacterial pathogen with or without growth of normal flora or (2) rare or no PMN cells and a pure culture of a pathogen. We excluded patients for whom respiratory culture specimens were not obtained within 48 hours of collection of positive viral specimen or if Gram-stained smear of specimen was not performed.

Review of the patient chart and clinical and administrative databases were conducted to collect information on patient characteristics, clinical data, and laboratory and radiological results. To evaluate semiquantitative information provided by examination of the Gram-stained smear, we created two ordinal variables: Gram-stained smear: PMN cells (GSS-PMN) and Gram-stained smear: bacteria (GSS-B) based on the interpretation guidelines followed by the Microbiology Laboratory at our institution (► **Table 1**). Review of radiological reports was conducted to assess for the presence of infiltrate on chest radiography as interpreted by a pediatric radiologist. We also identified patients with other chronic medical conditions associated with an increased risk of complications from viral respiratory illness.^{8–11} We measured severity of illness on admission to ICU using the Pediatric Index of Mortality 2 (PIM2).¹²

Our primary outcome of interest was bacterial coinfection, either probable or possible coinfection as defined earlier. We partitioned our dataset into an experimental (January to December 2010) and validation (January to December 2011). Univariate analyses were performed on the experimental dataset to assess association with bacterial coinfection. Variables with a *p*-value less than 0.05 in the univariate analysis were included in multivariable model construction.

We constructed multivariable models using probit regression to produce probability estimates that an individual patient does not have bacterial coinfection. Model coefficients were calculated using maximum likelihood estimation. Receiver operating characteristic (ROC) curve analysis was performed to assess discriminatory ability of the model. A final model was constructed using both experimental and validation datasets.

Continuous variables were compared using Student *t*-test or Wilcoxon rank-sum testing as appropriate. Normality of continuous variables was assessed by Shapiro–Wilk testing. Categorical and ordinal variables were compared using chi-square or Fisher exact testing as appropriate. Type I error was set at 0.05. All calculations were performed using Stata/IC 12.1 (Stata Corporation, College Station, Texas, United States).

Results

There were 175 patients with viral LRTI requiring invasive mechanical ventilation during the period of study. Forty-nine patients (28%) were excluded—15 patients had respiratory

Table 1 Gram-stained smear interpretation guidelines and score assignment

GSS-PMN/GSS-B score	Description	Number of PMN cells or organisms per OIF	Number of PMN cells or organisms per mL of specimen
0	None	None	None
1	Rare	<1 per 10 OIFs	<1,000
2	Few	1 to 10 per 10 OIFs	1,000 to 10,000
3	Moderate	1 to 10 per OIF	10,000 to 100,000
4	Many	>10 per OIF	>100,000

Abbreviations: GSS-B, Gram-stained smear–bacteria; GSS-PMN, Gram-stained smear–polymorphonuclear cells; OIF, oil immersion field; PMN, polymorphonuclear.

cultures obtained greater than 48 hours after collection of viral specimen and 34 patients were excluded due to lack of respiratory culture or Gram-stained smear. Of the 126 patients who met inclusion criteria, the breakdown by virus was as follows: RSV, 39 patients (31%); hMPV, 17 patients (14%); adenovirus, 23 patients (18%); and HRV/EB, 47 patients (37%). The median time interval between viral specimen and bacterial specimen collection was 0 days (interquartile range [IQR], 0–1 day).

The median age of patients was 20 months (IQR, 7 months to 4 years). Fifty-eight percent of patients were male. Sixty patients (48%) had a chronic medical condition with an increased risk of complications from viral respiratory illness including 27 patients (21%) with chronic respiratory disease, 24 patients (19%) with neuromuscular disease, and 8 patients (6%) with cyanotic heart disease.

The overwhelming majority of patients (93%) were admitted to the ICU with acute respiratory failure or insufficiency in the setting of acute infectious respiratory illness—eight patients (6%) were admitted following surgery for congenital heart disease and one patient (1%) was admitted in status epilepticus. Eighty-five patients (67%) received invasive mechanical ventilation on, or within 1 hour of, ICU admission. The median ICU and hospital lengths of stay were 12 days (IQR, 5–21 days) and 15 days (IQR, 8–32 days), respectively. The median number of ventilator days was 7 (IQR, 3–13 days). Predicted mortality on ICU admission by PIM2 was 3% (IQR, 0.9–6%). Thirteen patients did not survive to hospital discharge. The primary cause of death was multiorgan system failure in 10 patients and respiratory failure in 3 patients.

Thirty-eight patients met criteria for bacterial coinfection—31 with possible coinfection and 7 with probable coinfection. Patient characteristics stratified by bacterial coinfection are presented in ▶Table 2. Antibiotics were initiated in 117 patients (93%). Among the group without coinfection (88 patients), antibiotics were continued beyond 48 hours in 64 patients (72%) with a median duration of therapy of 7 days (IQR, 2–10 days). Seventy-six percent of patients that received antibiotics were administered two or more different classes

of antibiotics. The most common antibiotics administered were cephalosporins (71% of patients that received antibiotics), vancomycin (56%), penicillin (18%), clindamycin (11%), and meropenem (10%).

We performed univariate analyses on the experimental dataset (72 patients). Microbiological variables associated with bacterial coinfection included both GSS-PMN and GSS-B. The median GSS-PMN score was 3 for patients with bacterial coinfection and 2 for patients without ($p = 0.001$). The median GSS-B score was 2 for patients with bacterial coinfection and 0 for patients without ($p < 0.001$). Several clinical and demographic factors were not associated with bacterial coinfection in the experimental dataset including patient age, gender, infiltrate on chest radiography, absolute neutrophil count, chronic medical conditions, tracheostomy in situ, and severity of illness on ICU admission.

We included GSS-PMN and GSS-B in the construction of the experimental probit model. Coefficients for the experimental model are presented in ▶Table 3. By ROC curve analysis, area under the curve (AUC) = 0.8151 for the experimental dataset in discriminating bacterial coinfection. Testing the experimental model using the validation dataset yields an AUC = 0.8728. While not significant in the initial univariate analysis employing only the experimental dataset, patients with tracheostomies were noted to be more likely to have bacterial coinfection when the experimental and validation datasets were combined. As such, the variable tracheostomy in situ was included in the recalibrated model. Coefficients were calculated using both the experimental and validation datasets to construct a recalibrated model (▶Table 3). By ROC curve analysis, AUC = 0.8696 for the recalibrated model (▶Fig. 1).

We created a simplified model with two variables—presence of tracheostomy (yes/no) and a summary variable derived from the summation of the GSS-PMN and GSS-B scores (minimum score = 0, maximum score = 8). By ROC curve analysis, AUC = 0.8677 for the simplified model in discriminating bacterial coinfection (▶Fig. 1). If we restrict to only cases that meet the definition for probable bacterial coinfection, model discrimination improves with AUC = 0.9028.

Table 2 Characteristics of patients stratified by bacterial coinfection

Characteristic	Coinfection ($n = 38$)	No coinfection ($n = 88$)	p -Value
Age (mo)	18 (IQR, 6–60)	21 (IQR, 8–50)	0.98
Female gender	13 (34%)	40 (45%)	0.24
Chronic medical condition	18 (47%)	41 (47%)	0.94
Tracheostomy in situ	11 (29%)	9 (10%)	0.01
ICU LOS (d)	11 (IQR, 4–17)	12 (IQR, 5–24)	0.32
Hospital LOS (d)	15 (IQR, 7–28)	16 (IQR, 9–34)	0.34
Ventilator days	6 (IQR, 3–11)	7 (IQR, 3–14)	0.40
Antibiotic days	7 (IQR, 5–10)	7 (IQR, 2–10)	0.18
PIM2 predicted mortality (%)	2.8 (IQR, 0.9–4.1)	3.3 (IQR, 0.9–7.6)	0.36
Case fatality	3 (8%)	10 (11%)	0.75

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; PIM2, Pediatric Index of Mortality 2.

Table 3 Model coefficients for experimental, recalibrated, and simplified probit regression models on probability of no bacterial coinfection

Variable	Experimental model	Recalibrated model	Simplified model
GSS-PMN	−0.36189	−0.45377	–
GSS-B	−0.40243	−0.48216	–
Tracheostomy in situ	–	−0.88635	−0.89391
Summary ^a	–	–	−0.47040
Constant	1.87241	2.30468	2.33252

Abbreviations: GSS-B, Gram-stained smear–bacteria; GSS-PMN, Gram-stained smear–polymorphonuclear cells.

^aSummary variable equals the sum of the values of GSS-PMN and GSS-B variables.

► **Table 4** depicts the distribution of cases and model probability estimates based on the simplified score derived from GSS-PMN and GSS-B scores and partitioned by presence or absence of a tracheostomy. Among the 106 patients without tracheostomies, 47 (44%) had simplified scores of 2 or less, which equated to a model probability of no bacterial coinfection of 92%. Employing a cutoff of 2 or less would have missed zero cases of coinfection and identified 37 patients (79%) without coinfection who were treated with parenteral antibiotics for more than 48 hours (total antibiotic days = 379 days).

Discussion

Analysis of our results suggests that in children with viral LRTI requiring mechanical ventilation, a subset of patients at very low risk of bacterial coinfection can be identified by a mathematical modeling approach.

There has been considerable debate as to definitions of respiratory tract infection and factors that help to distinguish between viral and bacterial etiologies.¹³ We sought to overcome some of the uncertainty that exists in this area by limiting our focus to children with documented viral LRTI requiring mechanical ventilation, allowing for more accurate determination of bacterial coinfection.

Fig. 1 Receiver operating characteristic curves for the recalibrated and simplified models.

Overuse of antibiotics has contributed to the emergence and selection of drug-resistant organisms, which the World Health Organization described in 2014 as “a problem so serious that it threatens the achievements of modern medicine.”^{6,14} Implicit in our primary objective is that the identification of patients at very low risk of bacterial coinfection could lead to a decrease in antibiotic utilization in this cohort. While the use of a clinical decision tool to distinguish between viral bacterial pneumonia in an outpatient setting decreased antibiotic utilization, it is not clear how a modeling approach similar to ours would be received when the patient population were critically ill children.¹⁵ Our group is currently pursuing efforts to assess the threshold of risk tolerance toward early discontinuation of antibiotics among pediatric critical care practitioners in children at very low risk of bacterial coinfection.

Analysis of our results suggests that the presence of a tracheostomy is an independent risk factor for bacterial coinfection in children with severe LRTI requiring mechanical ventilation. Interestingly, of the 11 cases of bacterial coinfection among children with tracheostomies, only 1 case met criteria for probable coinfection. The diagnosis of bacterial coinfection in children with tracheostomies may be confounded by the high rates of bacterial colonization observed in this subset of patients. While risk stratification may be helpful in guiding therapy, attention to other factors (e.g., previous culture data) should be paid to help distinguish colonization from coinfection.

Our study was subject to several limitations, including the retrospective single-center study design. Unlike catheter-associated bloodstream infections for which a formal definition exists, diagnosis of pulmonary bacterial infection lacks a gold standard. In the absence of a gold standard, we chose to employ a previously published definition of both probable and possible pulmonary bacterial coinfection.^{3,5} As the definition of possible coinfection likely includes several children with bacterial colonization of the respiratory tract, it is not unreasonable to suggest that our rate of coinfection was overestimated. Given that the objective of this study was to identify children at very low risk of bacterial coinfection, we wanted to create a conservative model, as the cost of misidentifying a child at high risk of bacterial coinfection as very low risk could be considerable.

Table 4 Distribution of bacterial coinfection cases and model probabilities based on summary variable cutoffs

Summary value ^a	Total patients	Total coinfections (possible/probable)	Model probability of no bacterial coinfection (%)
No tracheostomy			
0	4	0	99
≤ 1	25	0	97
≤ 2	47	0	92
≤ 3	69	7 (7/0)	82
≤ 4	84	13 (12/1)	67
≤ 5	92	15 (13/2)	49
≤ 6	97	18 (15/3)	31
≤ 7	101	22 (19/3)	17
≤ 8	106	27 (21/6)	8
Tracheostomy			
0	1	0	92
≤ 1	5	1 (1/0)	83
≤ 2	8	3 (3/0)	69
≤ 3	10	4 (4/0)	51
≤ 4	14	7 (7/0)	33
≤ 5	15	7 (7/0)	18
≤ 6	19	10 (9/1)	8
≤ 7	19	10 (9/1)	8
≤ 8	20	11 (10/1)	1

^aSummary variable equals the sum of the values of the variables Gram-stained smear polymorphonuclear cells (0–4) and bacteria (0–4).

Variables derived from the interpretation of the Gram-stained smear contributed wholly to our model estimates. While the categorization of PMN cells and bacteria seen on Gram-stained smear are largely similar among microbiology laboratories, some variability does exist, primarily in the distinction between moderate and many PMN cells and bacteria.¹⁵ Our interpretation guideline is similar to previously published guidelines, and should be considered conservative in its distinction between moderate and many PMN cells or bacteria.¹⁶ As such, institutions that employ a markedly different interpretation guideline would be advised to consider reevaluation of model coefficients prior to employing this proposed model.

Our prediction model identifies patients with viral LRTI requiring mechanical ventilation at very low risk of bacterial coinfection. This model has the potential to decrease antibiotic utilization without negatively impacting clinical outcome.

Note

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None.

Conflict of Interest

None.

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