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MAJOR ARTICLE

Development and Validation of a Model to Predict Growth of Potentially Antibiotic-Resistant Gram-Negative Bacilli in Critically Ill Children With Suspected Infection

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Background. Risk-based guidelines aid empiric antibiotic selection for critically ill adults with suspected infection with Gram-negative bacilli with high potential for antibiotic resistance (termed high-risk GNRs). Neither evidence-based guidelines for empiric antibiotic selection nor validated risk factors predicting high-risk GNR growth exist for critically ill children. We developed and validated a model for predicting high-risk GNR growth in critically ill children with suspected infection.

Methods. This is a retrospective cohort study involving 2 pediatric cohorts admitted to a pediatric intensive care unit (ICU) with suspected infection. We developed a risk model predicting growth of high-risk GNRs using multivariable regression analysis in 1 cohort and validated it in a separate cohort.

Results. In our derivation cohort (556 infectious episodes involving 489 patients), we identified the following independent predictors of high-risk GNR growth: hospitalization >48 hours before suspected infection, hospitalization within the past 4 weeks, recent systemic antibiotics, chronic lung disease, residence in a chronic care facility, and prior high-risk GNR growth. The model sensitivity was 96%, the specificity was 48%, performance using the Brier score was good, and the area under the receiver operator characteristic curve (AUROC) was 0.722, indicating good model performance. In our validation cohort (525 episodes in 447 patients), model performance was similar (AUROC, 0.733), indicating stable model performance.

Conclusions. Our model predicting high-risk GNR growth in critically ill children demonstrates the high sensitivity needed for ICU antibiotic decisions, good overall predictive capability, and stable performance in 2 separate cohorts. This model could be used to develop risk-based empiric antibiotic guidelines for the pediatric ICU.

Keywords. drug resistance; risk factors; pediatric intensive care unit; Gram-negative bacterial infections; critical illness.

Timely administration of empiric antibiotics to which the infecting pathogen is susceptible is a hallmark of successful management of suspected infections in critically ill adults and children. Failure to provide prompt, correct empiric antibiotics is associated with adverse outcomes in many conditions, including adult and pediatric septic shock, adult ventilator- and health care–associated pneumonia, and severe community-acquired pneumonia (CAP) in adults and children [1–8].

This is balanced against rising antibiotic resistance in health care [9]. Particularly concerning in critical care is rising resistance among Gram-negative bacilli (GNRs) such as *Pseudomonas* sp., *Klebsiella* sp., and *Stenotrophomonas* sp. This has made appropriate antibiotic selection more challenging in the setting of infection with these organisms, which are at high risk of being resistant to typical antibiotics that target GNRs [10–12]. We term these organisms "high-risk GNRs." Prescribing extremely broad-spectrum antibiotics to intensive care unit (ICU) patients with suspected infection may ensure initial empiric correctness but would unnecessarily expose patients to medication side effects and could accelerate development of antibiotic resistance.

To allow both antibiotic stewardship and the need for early, correct empiric antibiotics, guidelines have been developed to aid antibiotic selection for adults with suspected infection [13–15]. These use risk stratification for infection by potentially resistant bacteria and provide antibiotic choices based on these risk factors. Pediatric guidelines exist for CAP but do not address the potential for high-risk GNRs [16]. No clear guidelines exist for antibiotic selection in other severe pediatric infections (eg, sepsis, health care–associated pneumonia, and ventilator-associated pneumonia) in the United States.

There is a paucity of literature regarding factors associated with high-risk GNRs in children and no statistical models that predict increased risk for these pathogens [17, 18]. Such a model could aid in the development and testing of empirical antimicrobial prescribing strategies in critically ill children. We recently reported that nearly half of children admitted to our pediatric ICU (PICU) with cultures positive for a high-risk GNR presented from the community without recent hospital exposure

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[19]. Thus, strategies targeting these organisms only in nosocomial infections may lead to inappropriately narrow-spectrum empiric antibiotics in many patients with high-risk GNRs. We therefore conducted a retrospective cohort study to develop and validate a model for predicting growth of high-risk GNRs in clinical cultures from critically ill children using our previously published risk factors as a starting point.

METHODS

This study was conducted in the PICU at Nationwide Children's Hospital, a large quaternary care children's hospital with services including oncology, bone marrow transplantation, and solid organ transplantation. Data from a separate cardiothoracic ICU were not included. Data were collected from the electronic health record and represent temporally distinct derivation and validation data sets. The Institutional Review Board of Nationwide Children's Hospital approved this study with a waiver of informed consent.

Definitions

High-risk GNRs included *Pseudomonas*, *Acinetobacter*, *Enterobacter* species, *Klebsiella oxytoca,* extended-spectrum β-lactamase-producing species, and other GNRs that demonstrated resistance or intermediate susceptibility to antibiotics from more than 1 antibiotic class expected to cover these organisms. These selections were based on previous literature highlighting organisms for which antibiotic resistance was of particular concern and also on local antibiotic susceptibility patterns [11–13]. Immunosuppression was defined as having 1 or more of the following: malignancy, chemotherapy within the prior month, solid organ transplant, nonengrafted stem cell transplant, chronic immunosuppressive therapy, chronic corticosteroid therapy (≥0.5 mg/kg/d prednisone equivalent or ≥10 mg/d), acute corticosteroid therapy for >5 days in the past month, or underlying congenital or acquired immunodeficiency.

Derivation Cohort

For model derivation, we used our previously published cohorts, which were used to evaluate the impact of a PICU empiric antibiotic prescribing protocol [19]. These included subjects from all of 2004 (pre–protocol implementation) and 2007 (post–protocol implementation). All subjects had at least 1 culture obtained and were admitted to the PICU with suspected infection. Subjects were identified for screening using infection-related International Classification of Diseases, Ninth Revision (ICD-9) codes including those for sepsis, bacteremia, meningitis, tracheitis, pneumonia, and urinary tract infection. Only patients for whom intent to treat infection in the PICU was confirmed by record review were included. Multiple episodes could be included for a single patient if 2 investigators agreed that the episode represented new symptoms concerning for new infection.

Validation Cohort

For model validation, we created a new cohort that included all patients with at least 1 culture obtained who were admitted to the same PICU with suspected infection using identical infection-related ICD-9 codes over a later 1-year period (July 1, 2014, to June 30, 2015). Only patients for whom intent to treat infection in the PICU was confirmed by record review were included. Multiple episodes could be included for a single patient if the subsequent episode occurred off antibiotics (except prophylactic antibiotics) and involved new onset of symptoms concerning for infection. The requirement for symptoms occurring off antibiotics was added for the validation cohort both to make our inclusion more rigorous with regard to ensuring we were capturing distinct infectious episodes and to streamline our process for identifying these separate episodes.

Potential Predictors

We evaluated our published risk factors for inclusion as predictors for high-risk GNRs in critically ill children [19]. These included hospitalization >48 hours before onset of suspected infection; current or recent use of systemic antibiotics (>7 days within the past 6 weeks); chronic lung disease, including chronic structural lung disease (eg, cystic fibrosis, bronchopulmonary dysplasia) plus chronic mechanical ventilation other than nocturnal ventilation for obstructive sleep apnea; unrepaired or incompletely palliated congenital heart disease; immunosuppression (see earlier definition); residence in a chronic care facility; inpatient hospitalization within the past month; presence of an indwelling central venous catheter; prior history of high-risk GNRs; or history of prematurity in children <2 years old. Children with any previous positive culture with growth of high-risk GNRs were considered to meet the definition of prior history of high-risk GNRs. Due to suspicion that infants and patients admitted for viral respiratory infection might be at lower risk compared with others with similar risk factors, we included age <1 year and having viral testing done as potential protective factors.

Outcome Variable

The outcome used for model construction was growth of any high-risk GNR in cultures obtained at the onset of suspected infection from blood, urine, cerebrospinal fluid, pleural fluid, peritoneal fluid, abscess fluid, or the lower respiratory tract (tracheal aspirate, protected brush tracheal aspirate, bronchoalveolar lavage specimen).

Data Collection

In addition to the presence of predictors plus culture and susceptibility data for each episode, we collected data on age, sex, and illness severity at the time of ICU admission using the Pediatric Risk of Mortality III (PRISM III) score [20].

Sample Size Estimate

For our derivation cohort, we used our previously published cohort, which contained 556 infectious episodes, with 139 episodes growing high-risk GNRs. For validation, based on prior literature, we determined a need for at least 100 episodes with

growth of high-risk GNRs and at least 100 episodes without these pathogens to ensure adequate model power [21, 22]. In addition, based on this number and using the prevalence of high-risk GNRs found in our derivation cohort (25%), we estimated that we would have 80% power to estimate a target AUC of 0.7 (found in our derivation cohort) with a confidence interval width of ±0.06. To capture potential seasonal variability, we evaluated all patients for 1 calendar year, which comprised 525 infectious episodes and 114 episodes with high-risk GNRs. There were no missing data from either cohort for model development.

Model Development

We used multivariable logistic regression with backward stepwise selection to develop our prediction model. Candidate variables included the 12 potential predictors outlined above. Variables were removed if they did not significantly impact model goodness of fit, as assessed by Akaike's Information Criterion. Because a main goal was to develop a simple model that was straightforward for bedside use, we did not assess interactions or nonlinearity. The final model regression formula was transformed into a simpler score formula by scaling and rounding regression coefficients. A total score was calculated for each patient by summing each model variable's score. We further simplified the model by determining the optimal score threshold that would result in at least 95% sensitivity. This was used to classify patients as being at increased risk for high-risk GNRs vs low risk for high-risk GNRs. We selected a 95% sensitivity cutoff based on physician risk tolerance, with our local physician group being willing to prescribe inappropriately narrow empiric antibiotics to no more than 5% of critically ill patients with suspected infection.

Model performance at the derivation stage was evaluated for a model using the risk score and another using the simplified binary risk status. Area under the receiver operating characteristic curve (AUROC) was used to assess discrimination (ability to separate patients who grew a high-risk GNR from those who did not). Model calibration (concordance between predicted and true GNR status) was assessed using the Brier score. Sensitivity and specificity are also reported. As a sensitivity analysis, we repeated model derivation and performance assessments using only the initial episode per patient to rule out any differential influence of patients with multiple episodes.

We assessed internal validity using a bootstrap procedure to estimate the amount performance statistics might differ given a different sample. For bootstrap validation, 1000 samples of size n = 556 (size of derivation cohort) were drawn, each with replacement. The entire model derivation process (including variable selection and simplification) was repeated in each bootstrap replicate, and the resulting model performance parameters were recorded. Optimism (or bias) in the original sample was estimated by taking the difference between the original performance parameter and the mean of the bootstrap sampling distribution of that parameter.

Model Validation

Patients in the validation cohort were classified as being at high or low risk for high-risk GNRs based on the risk grouping found during model development. We then calculated the sensitivity, specificity, positive predictive value, negative predictive value, and AUROC for predicting high-risk GNR status in the new cohort. To evaluate the potential impact on antibiotic utilization, we compared the number of patients considered high risk (thus warranting empiric broad antipseudomonal antibiotics) for both our previously published 10-item risk factor set and our new 6-item set.

Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC) and R: A language and environment for statistical computing 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 556 infectious episodes from 489 patients were included in the derivation cohort, whereas 525 episodes from 447 patients were included in the validation cohort. Patient characteristics and risk factor distribution are shown in Table 1. A minority developed infection while hospitalized (169 [30%] of the derivation cohort and 151 [29%] of the validation cohort); most had suspected infection at hospital admission. The types of bacteria identified are shown in Table 2, and sites from which

Table 1. Population Characteristics and Risk Factors

	Derivation Cohort (n = 556)[a]	Validation Cohort (n = 525)[a]
Baseline characteristics		
Age, y[b,c]	4 (0.75–14)	5 (0.75–13)
Male sex[b]	249 (51)	242 (54)
Admission PRISM III[b,c]	5 (2–10)	6 (2–11)
Risk factors		
Hospital >48 h	169 (30)	151 (29)
Recent antibiotics	146 (26)	145 (28)
Chronic lung disease	80 (24)	92 (18)
Congenital heart disease	42 (8)	7 (1)
Immunosuppressed	59 (11)	94 (18)
Chronic care facility	24 (4)	23 (4)
Prior high-risk GNRs	146 (26)	125 (24)
Recent hospitalization	96 (17)	75 (14)
Central venous line	31 (6)	110 (21)
Prematurity	13 (2)	34 (6)
Age <1 y	172 (32)	140 (27)
Viral testing	203 (37)	385 (73)
Outcomes		
Culture +	323 (58)	325 (62)
High-risk GNR +	139 (25)	114 (22)

Data are reported on a per-episode basis unless otherwise noted. Values are reported as No. (%) unless otherwise noted.

Abbreviations: GNR, Gram-negative bacilli; PRISM III, Pediatric Risk of Mortality III.

[a]Number of infectious episodes.

[b]Data are per patient (n = 489 for the derivation cohort and 447 for the validation cohort).

[c]Expressed as median (interquartile range).

Table 2. Bacteria Identified in Culture Listed as the Percentage of Total Identified Organisms

Organism	Derivation Cohort, No. (%)	Validation Cohort, No. (%)	Combined Cohort, No. (%)
High-risk GNRs			
Pseudomonas sp.	99 (19.5)	78 (14.5)	177 (16.9)
Enterobacter sp.	21 (4.1)	16 (3.0)	37 (3.5)
Stenotrophomonas maltophila	14 (2.8)	16 (3.0)	30 (2.9)
Klebsiella oxytoca	13 (2.6)	12 (2.2)	25 (2.4)
Acinetobacter sp.	7 (1.4)	14 (2.6)	21 (2.0)
Other high-risk GNRs	27 (5.3)	19 (3.5)	46 (4.4)
Low-risk organisms			
Gram-negative bacteria	177 (34.9)	202 (37.5)	379 (36.2)
Gram-positive bacteria	126 (24.9)	167 (31.0)	293 (28.0)
Other pathogens[a]	23 (4.5)	15 (2.8)	38 (3.6)

Organisms identified from more than 1 site in a single infectious episode are only listed once.

Abbreviation: GNR, Gram-negative bacilli.

[a]Includes fungal pathogens and *Mycoplasma*.

positive cultures were obtained are shown in the Supplementary Data (Supplementary Table 1).

Six factors were independently associated with growth of high-risk GNRs in the derivation cohort—hospitalization for >48 hours before onset of suspected infection, hospitalization within the past 4 weeks, recent treatment with systemic antibiotics, presence of chronic lung disease, residence in a chronic care facility, and having previously grown high-risk GNRs. These final variables from our derivation cohort, including coefficients, odds ratios, and confidence intervals, are shown in Table 3, as is the risk score for each risk factor derived from our regression formula.

The initial complete regression model before stepwise selection, as well as univariate associations, is shown in Supplementary Table 2. The optimal score threshold resulting in a minimum model sensitivity of 95% was 35.5, meaning that patients would be considered at elevated risk for high-risk GNRs if they had any model risk factors. Therefore, for simplified binary risk classification, patients with any variable from Table 3 (individually or in combination) were considered at elevated risk. The relationship between the model score and the absolute risk for growth of high-risk GNRs is shown in the Supplementary Data (Supplementary Figure 1).

Table 3. Final Predictive Model for Growth of High-risk GNRs Including Derived Risk Scores From a Multivariable Logistic Regression Model

Risk Factor	Coefficient	OR	Lower CL	Upper CL	*P* Value	Score
Intercept	−2.8004					
Hospital >48 h	1.3785	3.969	2.299	6.853	<.0001	100
Recent antibiotics	0.8433	2.324	1.421	3.802	.0008	61
Chronic lung disease	1.1899	3.287	1.735	6.225	.0003	86
Chronic care facility	1.3091	3.703	1.387	9.887	.009	95
Prior high-risk GNRs	1.2029	3.33	2.005	5.529	<.0001	87
Recent hospitalization	1.0151	2.76	1.543	4.936	.0006	74

Abbreviations: CL, confidence limit; GNR, Gram-negative bacilli; OR, odds ratio.

Evaluation of the simplified binary model performance within the derivation cohort (Table 4) indicated good performance. Sensitivity was high by design (96.4%), with a specificity of 48%, and bootstrap analysis revealed little training bias. Our sensitivity analysis, in which we repeated model derivation and performance assessment using only the initial infectious episode per patient, provided nearly identical results, suggesting that including statistically correlated observations did not unduly influence our findings. When the simplified binary model was applied to our validation cohort (Table 4), sensitivity remained high (93%), specificity increased slightly (51%), and overall performance, as measured by AUROC and the Brier score, remained similar, all suggesting good model performance. When applied to our combined cohorts, simplified binary model use for empiric antibiotic selection would have resulted in broad antipseudomonal antibiotics being empirically prescribed in 61 fewer infectious episodes (an 8.5% relative reduction) compared with use of our initial 10-item risk factor set (719 episodes vs 658 episodes) without resulting in inappropriately narrow antibiotic coverage. If compared with a PICU empiric antibiotic strategy prescribing broad antipseudomonal antibiotics initially for all patients (achieving 100% sensitivity), our 6-item risk factor set would result in broad antibiotics being prescribed in >400 fewer infectious episodes (658 vs 1081)—a 39% reduction in prescriptions.

DISCUSSION

Using 2 large, independent PICU cohorts, we have developed and validated a predictive model for growth of high-risk GNRs in critically ill children with suspected infection. This model is simple to use, provides the high sensitivity needed for empiric antibiotic selection in critically ill patients, and maintains enough specificity to limit unnecessarily broad antibiotics for many PICU patients. Our internal and external validation demonstrated that our risk model is not overfitted; the performance in the validation cohort was nearly identical to the derivation cohort despite being separated by nearly 10 years.

This study focuses on the epidemiology of pathogen growth in culture, not the presence or absence of infection. Adjudication of true infection can be difficult in critical illness, and it was not our intent to differentiate infection from colonization [23]. Rather, we intend to provide clinicians a tool to gauge a potentially infected patient's risk for harboring high-risk GNRs. If the clinician decides to treat empirically based on clinical judgment, this tool could guide more informed antibiotic prescription.

To our knowledge, this is the first validated predictive model for high-risk GNRs in critically ill children with suspected infection. The identified risk factors are objective and easily measured. Prior studies have evaluated risk of hospital-acquired

Table 4. Predictive Model Performance in Derivation and Validation Cohorts Including Bootstrap-Estimated Training Bias for the Derivation Cohort

	All Events[a]			First Event[b]		
Statistic	Derivation	Bias	Validation	Derivation	Bias	Validation
AUC	0.72 (0.69–0.75)	–0.024	0.72 (0.69–0.75)	0.73 (0.70–0.77)	–0.051	0.74 (0.70–0.78)
Brier	0.16 (0.15–0.17)	0.004		0.14 (0.12–0.16)	0.006	
Sensitivity	0.96 (0.93–1.0)	–0.019	0.93 (0.88–0.98)	0.95 (0.89–0.98)	–0.014	0.91 (0.82–0.96)
Specificity	0.48 (0.43–0.53)	–0.03	0.51 (0.46–0.56)	0.52 (0.47–0.57)	–0.087	0.58 (0.53–0.63)
PPV	0.38 (0.33–0.43)	–0.021	0.35 (0.29–0.40)	0.34 (0.28–0.39)	–0.025	0.34 (0.28–0.40)
NPV	0.98 (0.95–1.0)	–0.016	0.93 (0.94–0.99)	0.98 (0.95–1.0)	–0.017	0.96 (0.94–0.99)

"Derivation" values are estimated from the final derivation model. "Bias" values are bootstrap estimates of the amount by which the given parameter would change in a new cohort, and they are a measure of internal validity. "Validation" values are estimated from the validation cohort.

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

[a]Primary analysis, including all infectious episodes.

[b]Sensitivity analysis, including only the first infectious episode per patient.

infection, risk of colonization with these pathogens, or have evaluated antibiotic strategies using nonvalidated risk factors [19, 24–27]. Given the lack of PICU-specific guidelines, validated risk factors are important to aid empiric antibiotic selection and stewardship. Early correct empiric antibiotics can improve outcomes in critically ill children with suspected infection, whereas antibiotic stewardship is equally important to limiting development of antibiotic resistance. This balance is discussed in the recent adult ventilator-associated pneumonia guidelines [6, 8, 14]. Our validated risk factors could serve as a foundation for empiric antibiotic strategies in critically ill children, taking into account both these concerns by restricting broad antipseudomonal antibiotics to only those determined more likely to grow high-risk GNRs rather than basing these antibiotic decisions on illness severity.

Use of clinical factors to aid risk assessment for specific pathogens is a component of many antibiotic guidelines, including adult guidelines for community- and hospital-acquired pneumonia [13–15]. Guideline-concordant antibiotic strategies can improve outcomes for critically ill adults [28–31]. Unfortunately, all current evidence-based ICU guidelines are for adults. This can lead to practice variability and inappropriate empiric antibiotic prescribing for critically ill children, which could worsen outcomes if empiric antibiotics are inappropriately narrow or increase antibiotic resistance, side effects, and cost if empiric coverage is too broad.

Our validated risk factors could be utilized to evaluate PICU-specific empiric antibiotic strategies. We have integrated these risk factors into antibiotic order sets, allowing risk assessment at initial antibiotic prescription. We previously showed that this strategy (with a broader risk factor set) improved empiric antibiotic appropriateness in our PICU [19]. Our current results imply that we could safely restrict empiric antipseudomonal agents further beyond our previously published strategy, which already provided a significant antibiotic stewardship benefit compared with an approach prescribing these very broad antibiotics to all critically ill patients based on illness severity. Given the success of adult guidelines, the success of our local guideline implementation, and the broader success of pediatric CAP guidelines in non-ICU patients, it seems reasonable to expect that similar risk-based strategies could improve the care of critically ill children with suspected infection [19, 28–34]. For these patients, current evidence suggests that there are opportunities for improvement both in prescribing broader-spectrum antibiotics for some patients and in prescribing narrower-spectrum agents for others [6, 8, 35]. We envision that our risk model could be incorporated into PICU empiric antibiotic strategies for an individual unit or as part of consensus antibiotic use strategies either as we have proposed (a single yes/no decision) or through calculation of individual risk for high-risk GNRs using individual model scores.

There are many strengths of our study and of our risk model. Our cohorts were large (particularly for a PICU study) and representative of a multidisciplinary PICU population. The risk factors were clearly defined and easily determined, and the outcome was concrete and objective. Our findings were statistically robust, and the model performed well in distinct populations separated by time. Our final model is simple to apply at the time of initial antibiotic selection and provides a yes/no prediction rather than requiring calculation and interpretation of a risk score. Although this can limit the nuance of a score, ease of use may enhance clinical feasibility. Our cohorts contained many children with complex conditions. Leyenaar et al. pointed out antibiotic challenges in these patients and proposed evaluation of similar antibiotic selection strategies in this group [36]. Further research is needed to evaluate our risk factor strategy for these children outside the PICU.

There are several limitations of our study. All patients were from a single center, potentially limiting the generalizability to other ICUs. It will be important to validate the risk model in a multicenter fashion. In addition, the risk factor prevalence in our cohorts may differ from other ICUs, and indeed, it differed between our derivation and validation cohorts. The stable model performance between our cohorts is reassuring in

this regard. Our cohorts had limited representation from some key populations, including those with congenital heart disease (1% of our validation cohort). This could limit generalizability, although this risk factor was not associated with growth of high-risk GNRs in the derivation cohort, which had a higher proportion of these patients. Interestingly, immunocompromise was not independently associated with growth of high-risk GNRs, perhaps because other better-performing risk factors were frequently in this population (eg, current or recent hospitalization [59%], recent systemic antibiotics [37%], prior high-risk GNRs [19%]). Additionally, a significant portion of our cultures were respiratory cultures, potentially skewing our model results due to over-representation. However, our breakdown of culture sources reflects typical ICU experience and is likely representative of infections encountered in the PICU [37]. Additionally, although some of our risk factors may seem obvious (prescribing antibiotics that cover high-risk GNRs to patients who have previously grown high-risk GNRs), our local experience is that prior microbiologic data are not always considered when making antibiotic decisions. Any model that excludes these obvious factors would be woefully incomplete.

Although the model had high sensitivity, the specificity was lower, resulting in AUROCs that were 0.722 and 0.720 for the derivation and validation cohorts, respectively. We suspect that specificity suffered because some subjects had negative cultures due to an inability to sample the likely true site of infection (eg, the lower respiratory tract in children receiving noninvasive ventilatory support). This could lead to an underestimate of specificity and a bias against our model through assignment of false negatives. Research is ongoing to evaluate the impact of these patients on model performance. A predictive model would have particular utility in this or other populations in which there are inadequate microbiologic data to guide antibiotic de-escalation. Also, we do report positive and negative predictive values for our cohorts, but it is important to note that these may differ in other populations because they depend on the prevalence of the outcome.

We suspected that infants and those with suspected viral infections would have reduced risk for growth of high-risk GNRs but were unable to demonstrate this, potentially due to sample size. Similarly, duration of hospitalization prior to infection was only available as a binary risk factor for the derivation cohort. This prevented us from evaluating the timing during a hospitalization at which increased risk for growth of high-risk GNRs may occur. Further studies are needed to further refine our risk factors related to these issues.

CONCLUSIONS

Antibiotic selection and management of suspected infections in the PICU require a balance between the need for timely antibiotics in critically ill patients and the need for good antibiotic stewardship. Our risk factor model provides a simple tool that effectively stratifies critically ill children with suspected infection into those at increased risk for growing high-risk GNRs and those for whom the risk is low. Further research is needed to validate these risk factors in other institutions and to evaluate their potential impact on broad-spectrum antibiotic utilization and patient outcomes in a multicenter fashion.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. T.K. has no conflicts of interest to declare. M.M.C. has no conflicts of interest to declare. M.H. has no conflicts of interest to declare. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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