A Decision Tree Using Patient Characteristics to Predict Resistance to Commonly Used Broad-Spectrum Antibiotics in Children With Gram-Negative Bloodstream Infections

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Background. As rates of multidrug-resistant gram-negative infections rise, it is critical to recognize children at high risk of bloodstream infections with organisms resistant to commonly used empiric broad-spectrum antibiotics. The objective of the current study was to develop a user-friendly clinical decision aid to predict the risk of resistance to commonly prescribed broad-spectrum empiric antibiotics for children with gram-negative bloodstream infections.

Methods. This was a longitudinal retrospective cohort study of children with gram-negative bacteria cared for at a tertiary care pediatric hospital from June 2009 to June 2015. The primary outcome was a bloodstream infection due to bacteria resistant to broad-spectrum antibiotics (ie, cefepime, piperacillin-tazobactam, meropenem, or imipenem-cilastatin). Recursive partitioning was used to develop the decision tree.

Results. Of 689 episodes of gram-negative bloodstream infections included, 31% were resistant to broad-spectrum antibiotics. The decision tree stratified patients into high- or low-risk groups based on prior carbapenem treatment, a previous culture with a broad-spectrum antibiotic resistant gram-negative organism in the preceding 6 months, intestinal transplantation, age ≥ 3 years, and ≥ 7 prior episodes of gram-negative bloodstream infections. The sensitivity for classifying high-risk patients was 46%, and the specificity was 91%.

Conclusion. A decision tree offers a novel approach to individualize patients' risk of gram-negative bloodstream infections resistant to broad-spectrum antibiotics, distinguishing children who may warrant even broader antibiotic therapy (eg, combination therapy, newer β -lactam agents) from those for whom standard empiric antibiotic therapy is appropriate. The constructed tree needs to be validated more widely before incorporation into clinical practice.

Keywords. Antibiotic stewardship; multidrug-resistant gram-negative organisms; recursive partitioning; bloodstream infections.

Bloodstream infections are an important cause of disease and death among children [1–4]. Children with indwelling vascular catheters, which may be required for administration of chemotherapy or parenteral nutrition, are at an especially high risk for developing bloodstream infections [1, 2, 5–10]. In children for whom there are heightened concerns about bloodstream infections, empiric treatment is often started with broad-spectrum antibiotic agents, such as cefepime, piperacillin-tazobactam,

meropenem, or imipenem-cilastatin, rather than agents without pseudomonal activity. Because multidrug-resistant gram-negative (MDRGN) organisms are a growing threat in children [11–13], and children infected with these organisms have a higher risk of infection-associated death [14–16], there is likely a subpopulation of children who may benefit from broader empiric therapy (eg, combination therapy or newer β -lactam- β -lactamase inhibitors). This is particularly relevant because delays in appropriate empiric antibiotic therapy have been associated with poorer clinical outcomes [17, 18]. Equally important, it is critical to identify children at low risk for resistant infections to avoid unnecessary antibiotic exposure when these drugs will not offer added benefit but carry the risk of additional adverse events and development of antibiotic resistance.

Studies in the pediatric population have generally identified clinical factors associated with MDRGN infections using regression analysis [19–22]. To date, there have not been prediction tools, such as a risk score derived from a regression model

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or classifier derived from a decision tree, to aid in determining whether an individual child is infected with a MDRGN organism. Risk scores and decision trees have been developed in adult populations, but they have focused on identifying the risk of a particular mechanism of resistance (eg, Enterobacteriaceae producing extended-spectrum β -lactamases [ESBLs]) or have included the causative organism in the prediction algorithm [23–28]. Therefore, these prediction tools have limited value when a Gram stain reveals a gram-negative organism in a blood culture, but the pathogen and associated resistance patterns remain unknown. The objective of the current study was to develop a user-friendly clinical decision aid for children identified as having a gram-negative bloodstream infection to predict the risk of resistance to common broad-spectrum antibiotics and inform empiric antibiotic selection.

METHODS

Study Design and Setting

A retrospective cohort study was conducted at the Children's Hospital of Pittsburgh (CHP), a freestanding 315-bed tertiary care pediatric hospital in Pittsburgh, Pennsylvania. The study included all patients admitted to CHP from June 2009 through June 2015 with ≥ 1 blood culture, obtained from a peripheral or a central catheter source, in which gram-negative bacteria grew. Patients were excluded if they were not admitted to the hospital or if insufficient antibiotic susceptibility information was available. Uniformly susceptible respiratory pathogens (eg, *Haemophilus influenzae*), pathogens primarily associated with gastroenteritis (eg, *Salmonella* and *Shigella* species), and organisms intrinsically resistant to cefepime or piperacillin-tazobactam (CPT) (eg, *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia*) were excluded.

Outcome Measures and Definitions

An episode of bacteremia was defined as a positive blood culture identified ≥ 30 days after the last positive blood culture with that same organism. If a different gram-negative organism was identified from a blood culture before this period, it was considered a separate episode (eg, culture with *Escherichia coli* growing 12 days later if *Klebsiella pneumoniae* grew in initial culture). The most resistant susceptibility pattern was used if cultures were polymicrobial with gram-negative organisms. The primary outcome was a bloodstream infection with a gram-negative organism resistant to broad-spectrum antibiotics (BSAs) that would require escalation of antibiotic treatment. Specifically, BSA resistance was defined as a culture that (1) was nonsusceptible to either cefepime, piperacillin-tazobactam, meropenem, or imipenem-cilastatin or (2) met criteria for ESBL production [29]. We determined this definition of resistance a priori because we believed it was more clinically applicable than conventional definitions of MDRGNs [30]. Carbapenem

resistance was included in the composite outcome rather than characterized independently from cefepime and piperacillin-tazobactam resistance, because there were not enough instances of carbapenem resistance to analyze independently, and excluding carbapenem resistant infections would incur significant exclusion bias.

Cohort Development and Data Collection

Children with gram-negative organisms growing in blood cultures were identified using CHP's microbiology database. Demographic, clinical, and microbiological data were queried from CHP's data warehouse. Preexisting conditions were based on the *International Classification of Diseases, Ninth Revision*. Missing data were collected by manual chart review, as were (1) prior clinical cultures from any source with gram-negative organisms that were nonsusceptible to CPT or carbapenems (evaluated separately) in the preceding 6 months, (2) mechanical ventilation within 48 hours after the culture, (3) vasopressors within 48 hours after the culture, and (4) country of birth. Country of birth was used as a surrogate for international exposure.

Children with intestinal transplants have a high risk of repeat bloodstream infections [31], and not all centers may perform intestinal transplantations; therefore, these were distinguished from other types of solid organ transplantation. Most variables were represented by a continuous scale, and we permitted the decision tree to generate meaningful cutoff values. However, the number of prior admissions was converted into ordinal categories for end-user ease of use. Similarly, days of antibiotic exposure any time within the prior 6 months was dichotomized at ≥ 7 days of treatment, because this was likely to reflect a prior treatment course. The University of Pittsburgh Medical Center Institutional Review Board approved the study, with a waiver of informed consent.

All clinical specimens were processed in the CHP microbiology laboratory. Organism identification and antibiotic susceptibilities were ascertained by the Microscan automated system (MicroScan WalkAway 96; Siemens), according to contemporaneous Clinical and Laboratory Standards Institute recommendations [32].

Statistical Analysis

Descriptive statistics for patient variables were calculated using means (with standard deviation) for continuous data, medians (with interquartile ranges) for continuous skewed data, and frequencies (with percentages) for categorical or binary data. For patients with multiple episodes of bacteremia, BSA resistance for adjacent episodes was tabulated and data compared using the Fisher exact test. Few studies have evaluated gram-negative resistance among longitudinal cohorts. Therefore, we initially evaluated the associations between the a priori selected clinical risk factors and the outcome of BSA resistance using

logistic regression. To account for the fact that some patients had multiple episodes of bloodstream infections within the data set, the models were fit using generalized estimating equations, assuming an exchangeable correlation structure within patient and robust variance estimate [33]. Risk factors were examined by means of univariable logistic regression, and then all variables were included in the final multivariable model. The results were summarized as odds ratios with associated 95% confidence intervals. Predictive covariates had the potential to be interrelated. The variance inflation factor was calculated, and there was no indication of collinearity of the independent variables. These descriptive and regression analyses were performed using Stata software (version 14.0; StataCorp).

Regression-based prediction tools have been developed to predict resistance in the adult literature, and offer the advantage of producing an individual patient “risk score” to be used by clinicians to flag patients at high risk for resistance [24, 27, 28]. However, regression-based approaches rely on the ability to appropriately model the risk of resistance as a function of the clinical risk factors; this includes correctly specifying the form of the relationships between resistance and the clinical risk factors (eg, linear, quadratic, or discretizing continuous variables at appropriate thresholds) and necessary interactions between clinical risk factors. Recursive partitioning can accommodate these concerns and produces a binary classification of “high risk” versus “low risk” for BSA resistance.

Therefore, a decision tree was constructed using methods similar to those of Goodman and colleagues [23]. The tree was built using the “rpart” package (Recursive Partitioning and Regression Trees) in R software, version 4.3.4. All predictor variables were assessed to determine whether they would contribute to improved discrimination of the decision tree. The variable that best minimized misclassification of the outcome by the Gini splitting index was used to split the data set into lower- and higher-risk groups (“nodes”) [34]. This procedure was repeated in each daughter node. The tree stopped at the final groups, “terminal nodes,” when additional splits did not further reduce misclassification. Within terminal nodes, the correct classification of observations was assessed, yielding a probability of resistant infection. The decision tree was internally validated using leave-one-out cross-validation. The discriminatory capability of the model was evaluated using receiver operating characteristic curves and C statistics in R software.

RESULTS

Of 703 episodes of gram-negative bloodstream infections that met eligibility criteria, 14 were excluded owing to patients not being hospitalized or insufficient susceptibility data. We evaluated 689 episodes of gram-negative bloodstream infections, occurring among 387 patients and during 638 hospital admissions. The majority of patients (n = 275) experienced 1 episode

of bacteremia. One patient had 24 bloodstream infection episodes. Of the 689 episodes, 38% were polymicrobial, and >1 gram-negative organism grew in 17%. Table 1 presents the distribution of gram-negative organisms recovered.

Resistance Patterns

Of the 689 episodes, 217 (32%) were categorized as BSA resistant. Among all 689 episodes, 142 (21%) were resistant to cefepime, 189 (27%) to piperacillin-tazobactam, 114 (17%) to both cefepime and piperacillin-tazobactam, and 57 (8%) to meropenem or imipenem-cilastatin. Among patients with >1 episode of gram-negative bacteremia, it was more likely that the subsequent episode was BSA resistant if the prior episode was also BSA resistant (n = 106) than if the prior episode was non-resistant (n = 196) (59% vs 30%; $P \leq .001$).

Clinical Characteristics and Logistic Regression

Overall, the cohort was predominantly white (77%) and evenly distributed by sex (55% male), and the median age was 2.4 years (interquartile range, 0.9–8 years). The clinical characteristics of patients at the time of culture, stratified by BSA-resistant status, are summarized in Table 2. In univariable analyses, variables with higher odds of BSA resistance included Asian race, increasing age, intestinal transplantation, mechanical ventilation, intensive care unit admission, prior culture from any source with CPT resistance within the preceding 6 months, number of prior hospital admissions, number of prior gram-negative bloodstream infections, days in the hospital preceding blood culture collection (distinguishing community onset from onset after cumulative hospital exposure), and prior carbapenem therapy.

The multivariable model, presented in Table 3, included all variables evaluated in univariable analysis, because these were chosen a priori as potentially having an impact on the outcome of resistance. The variables that remained significantly associated with resistant infection in multivariable analysis included

Table 1. Distribution of Gram-Negative Bacteria Causing Bloodstream Infections in a Cohort of Children Hospitalized at the Children's Hospital of Pittsburgh, 2009–2015

Organism	Frequency, No. (%)
<i>Klebsiella</i> species	283 (34.3)
<i>Escherichia</i> species	202 (24.5)
<i>Enterobacter</i> species	147 (17.8)
<i>Pseudomonas aeruginosa</i>	66 (8.0)
<i>Serratia</i> species	47 (5.7)
<i>Acinetobacter</i> species	29 (3.5)
<i>Citrobacter</i> species	15 (1.8)
<i>Proteus mirabilis</i>	13 (1.6)
<i>Morganella morganii</i>	8 (1.0)
Other gram-negative organisms ^a	8 (1.0)
<i>Achromobacter</i> species	7 (0.9)

^aOther gram-negative organisms included *Chryseobacterium meningosepticum*/Flavobacterium (n = 2), *Pantoea agglomerans* (n = 5), and *Aeromonas hydrophila* (n = 1).

Table 2. Clinical Characteristics of Children With Gram-Negative Bloodstream Infections by BSA Resistance Status^a

Clinical Characteristic	Children, No. (%) ^b		Odds Ratio (95% CI)	P Value
	Nonresistant Infection (n = 472; 68.5%)	BSA-Resistant Infection (n = 217; 31.5%)		
Female sex	200 (42.4)	107 (49.3)	1.25 (.85–1.85)	.26
Race				
White	358 (75.8)	171 (78.8)	Reference	...
Black	92 (19.5)	30 (13.8)	0.86 (.50–1.49)	.60
Asian	10 (2.1)	9 (4.1)	3.05 (1.07–8.68)	.04
Other	12 (2.5)	7 (3.2)	1.70 (.64–4.51)	.28
Age at time of culture, median (IQR), y	2.1 (0.7–6.7)	3.7 (1.5–9.8)	1.03 (1.00–1.06)	.03
Place of birth outside United States ^c	26 (5.5)	26 (12.0)	1.96 (.97–3.93)	.06
Preexisting medical condition				
Cancer	53 (11.2)	12 (5.5)	0.62 (.29–1.29)	.20
Hematopoietic stem cell transplantation	37 (7.8)	13 (6.0)	0.96 (.45–2.07)	.93
Congenital cardiac disease	24 (5.1)	7 (3.2)	1.03 (.41–2.60)	.94
Intestinal insufficiency	146 (30.9)	66 (30.4)	1.36 (.81–2.28)	.24
Intestinal transplantation	38 (8.1)	55 (25.3)	3.55 (2.04–6.16)	<.001
Other solid organ transplantation	22 (4.7)	10 (4.6)	1.51 (.69–3.29)	.31
Other diagnoses	152 (32.2)	54 (24.9)	Reference	...
Central catheter	368 (78.0)	189 (87.1)	1.57 (.98–2.54)	.06
Vasopressors	60 (12.7)	39 (18.0)	1.44 (.92–2.26)	.11
Mechanical ventilation	81 (17.2)	57 (26.3)	1.77 (1.19–2.64)	.005
Admitted to the intensive care unit ^d	215 (45.6)	125 (57.6)	1.47 (1.07–2.01)	.02
Culture with CPT resistance within 6 mo	78 (16.5)	97 (44.7)	2.78 (1.92–4.01)	<.001
Culture with carbapenem resistance within 6 mo	22 (4.7)	28 (12.9)	1.66 (.88–3.13)	.12
No. of prior admissions ^e				
0	111 (23.5)	34 (15.7)	Reference	...
1–4	129 (27.3)	36 (16.6)	0.93 (.55–1.59)	.79
5–9	95 (20.1)	40 (18.4)	1.28 (.73–2.23)	.40
10–14	43 (9.1)	30 (13.8)	2.10 (1.14–3.88)	.02
≥15	94 (19.9)	77 (35.5)	2.27 (1.31–3.93)	.003
Time since previous hospital discharge, median (IQR), mo	0.0 (0.0–2.0)	0.0 (0.0–1.0)	1.00 (.96–1.04)	.91
Prior gram-negative bloodstream infections, median (IQR), No.	0.0 (0.0–1.0)	1.0 (0.0–3.0)	1.13 (1.03–1.24)	.008
Time in hospital before blood culture collection, median (IQR), d ^f	0.0 (0.0, 11.5)	1.0 (0.0, 20.0)	1.01 (1.00–1.01)	.006
Antibiotic therapy ≥7 d within 6 mo				
3rd-Generation cephalosporin	63 (13.3)	24 (11.1)	1.01 (.63–1.65)	.95
Cefepime	105 (22.2)	53 (24.4)	1.21 (.80–1.83)	.37
Piperacillin-tazobactam	216 (45.8)	128 (59.0)	1.46 (1.03–2.06)	.03
Carbapenem	51 (10.8)	83 (38.2)	4.20 (2.78–6.33)	<.001
Fluoroquinolone	45 (9.5)	37 (17.1)	1.41 (.88–2.26)	.15

Abbreviations: BSA, broad-spectrum antibiotic; CI, confidence interval; CPT, cefepime or piperacillin-tazobactam; IQR, interquartile range.

^aBSA resistance was defined as resistance to cefepime, piperacillin-tazobactam, or carbapenems.

^bData represent No. (%) of children unless otherwise specified.

^cAmong the 14 patients born outside the continental United States, birth countries included Puerto Rico (n = 5), Qatar (n = 3), and Egypt, Guatemala, Kuwait, Norway, Oman, and Russia (each n = 1).

^dAdmitted to the intensive care unit during the admission for that episode.

^eThe median number of prior hospital admissions was 4.0 (IQR, 1.0–11.0) in the nonresistant group versus (2.0–20.0) in the BSA-resistant group.

^fThe proportion of cultures obtained within the day of admission was 61.9% in the nonresistant group versus 55.3% in the BSA-resistant group.

intestinal transplantation (odds ratio, 2.73; 95% confidence interval, 1.62–4.59), prior culture with a CPT-resistant organism within 6 months (1.94; 1.18–3.19), number of prior gram-negative bloodstream infections (1.07; 1.01–1.13), and prior treatment with a carbapenem within 6 months (2.74; 1.54–4.88).

Decision Tree

The decision tree, developed using binary recursive partitioning, classifies the gram-negative bloodstream infections as high risk for an isolate qualifying as BSA resistant versus low risk

(Figure 1). After evaluation of all data set variables, the tree included 5 clinical risk factors in order of discriminatory potential: whether the patient had previously been treated with a carbapenem for ≥7 days, prior culture with CPT resistance within 6 months, intestinal transplantation, ≥7 prior episodes of gram-negative bloodstream infections, and age ≥3 years. The tree classified the majority of bloodstream infections (n = 460) as low risk for BSA resistance; this group included bloodstream infections for patients who had not been recently treated with

Table 3. Multivariable Adjusted Odds Ratios of Broad-Spectrum Antibiotic Resistance Among Children With Gram-Negative Bloodstream Infections^a

Patient Characteristic	Odds Ratio (95% CI)	P Value
Female sex	1.33 (.82–2.17)	.25
Race		
White	Reference	...
African American	1.05 (.58–1.92)	.87
Asian	1.98 (.53–7.45)	.31
Other	1.57 (.28–8.88)	.61
Age at time of culture (y)	1.00 (.97–1.03)	.96
Born outside United States	0.69 (.36–1.30)	.25
Intestinal transplantation ^b	2.73 (1.62–4.59)	<.001
Central catheter	0.96 (.51–1.80)	.90
Vasopressors	1.06 (.60–1.87)	.84
Mechanical ventilation	1.36 (.72–2.57)	.34
Admitted to the intensive care unit	1.35 (.82–2.21)	.23
Culture with CPT resistance within 6 mo	1.91 (1.16–3.16)	.01
Culture with carbapenem resistance within 6 mo	1.09 (.52–2.26)	.82
Prior admissions ^c	1.18 (.97–1.43)	.10
Time since prior discharge (mo)	1.02 (.99–1.06)	.20
No. of prior gram-negative bloodstream infections	1.07 (1.01–1.13)	.02
Time in hospital before culture (d)	1.00 (1.00–1.01)	.04
Antibiotic therapy ≥7 d within 6 mo		
3rd-Generation cephalosporin	0.92 (.48–1.79)	.81
Cefepime	1.37 (.87–2.17)	.18
Piperacillin-tazobactam	1.04 (.67–1.61)	.88
Carbapenem	2.74 (1.54–4.88)	.001
Fluoroquinolone	0.77 (.39–1.52)	.45

Abbreviations: CI, confidence interval; CPT, cefepime or piperacillin-tazobactam.

^aBroad-spectrum antibiotic resistance defined as resistance to cefepime, piperacillin-tazobactam, or carbapenems.

^bIntestinal transplantation was analyzed as a binary variable (either undergoing intestinal transplantation or not), because other diagnostic groups did not show a relationship with the outcome in the univariable analysis shown in Table 1.

^cPrior admissions were analyzed as ordinal categories as shown in the univariable table in Table 2 (0, 1–4, 5–9, 10–14, or ≥15 prior admissions), because there was a dose-response relationship in the univariable analysis shown in Table 1.

a carbapenem, did not have a prior culture with CPT resistance within 6 months, and had <7 bloodstream infections.

Internal Validation and Sensitivity Analyses

Using leave-one-out cross validation, the sensitivity of the decision tree to classify patients at high risk of BSA-resistant infection was 46%, whereas the specificity of the tree was 91%, with an area under the curve of 0.70. Before cross-validation, the sensitivity, specificity, and area under the curve were 46%, 91%, and 0.68, respectively. The prevalence of BSA-resistant bloodstream infection was 31%, yielding a positive predictive value of 69% and negative predictive value of 78%. In the largest group of bloodstream infections, which were classified as low risk for BSA resistance ($n = 460$), 92 episodes were BSA resistant (20%). Overall, the tree misclassified 92 of the 217 total BSA-resistant episodes into this low-risk node, thereby contributing to the decision tree's suboptimal sensitivity.

To evaluate the robustness of our findings, we refit the data after removing the patient with 24 episodes of gram-negative

bacteremia. Both the multivariable regression trends and the decision tree remained relatively unchanged, except that the cutoff point for prior gram-negative bloodstream infections was reduced from 7 to 6 episodes. Because CHP has a relatively high volume of intestinal transplantation, we reanalyzed the data excluding patients undergoing intestinal transplantation. The variables included in the decision tree remained the same, and the decision pathway would be unchanged for most episodes (data not shown). The decision tree remained applicable to patients without a history of intestinal transplantation.

DISCUSSION

We present a decision tree that can assist clinicians with determining whether standard empiric therapy (ie, cefepime, piperacillin-tazobactam, meropenem, or imipenem-cilastatin) is sufficient or whether broader antibiotic therapy is warranted for children with gram-negative bloodstream infections. This decision tree can help guide antibiotic therapy at the time Gram stains from positive blood cultures indicate the presence of gram-negative organisms, and before the availability of organism or susceptibility data, ultimately, with the goal of optimizing patient outcomes by either escalating empiric therapy or avoiding unnecessary exposure to broader antibiotic therapy than is needed.

In the decision tree, prior carbapenem treatment, prior culture with a CPT-resistant organism, intestinal transplantation, age ≥3 years, and ≥7 prior gram-negative bloodstream infections were associated with increased risk of a resistant infection. These findings are congruent with clinical intuition: if a patient has recently received carbapenem therapy or had a resistant infection, he or she is at a higher risk of infection with a resistant organism and may benefit from broader empiric treatment approaches, such as combination therapy, extended-infusion β -lactam strategies, or novel β -lactam- β -lactamase inhibitor combinations, etc. Similar variables were associated with a higher risk of resistant bloodstream infection in both the adjusted regression model and the decision tree. Regression models can be used to generate risk scores that can offer individualized risk of resistance but depend on appropriately structuring models [24, 27, 28]. Some advantages of the decision tree approach are the ability to efficiently incorporate complex interactions, account for collinearity between variables, and generate easy-to-use cutoff values for continuous variables. In addition, decision trees avoid requiring computation of a composite score at the time of use.

Our decision tree had a high specificity (91%) but low sensitivity (46%) for detecting BSA resistance. The decision tree may misclassify close to 50% of high risk of BSA-resistant episodes as low risk and 9% as high risk, potentially leading to undertreatment or overtreatment, respectively. Owing to the relatively high prevalence of resistance in the cohort (31%), the

Figure 1. Decision tree illustrating the risk of broad-spectrum antibiotic (BSA) resistance among children with gram-negative bloodstream infections based on individual patient risk factors. This decision tree was developed by recursive partitioning and included analysis of all the predictor variables as shown in Table 3. The risk of BSA resistance presented as a percentage; BSA resistance is defined as resistant to cefepime, piperacillin-tazobactam or carbapenems. Gray hexagons represent nodes with high risk of BSA resistance; squares represent nodes, nodes with low risk of BSA resistance. Abbreviations: N, no; Y, yes.

positive predictive value was 69%. Therefore, if the tree places someone into a high-risk node, it is likely that the patient will be infected with a BSA-resistant organism. If the same decision tree is applied to a patient population with a lower resistance prevalence (eg, children admitted to community hospitals or hospitals whose patients have less resistant bacteria), the positive predictive value would decrease, but the negative predictive value (78%) would increase and better identify patients at low risk of BSA-resistant bloodstream infection.

Goodman and colleagues [23] developed a decision tree to assess the risk of ESBL bloodstream infections using an adult population. Similar to our tree, theirs misclassified a reasonable proportion of resistant episodes into a low-risk node. Both trees demonstrated that, even after accounting for several notable risk factors, the decision tree carries the risk of misclassification; a proportion of resistant infections will be classified as low risk and will not be foreseeable. Because the decision tree had a suboptimal sensitivity for detecting BSA-resistant infections, clinical judgment and deviations from tree predictions would be necessary when the implications of misclassification could be detrimental. For example, if a patient were critically ill or not improving with initial therapy, then escalation of antibiotics may be justified even if the patient was classified as low risk.

We provide 2 hypothetical scenarios to exemplify how the decision tree could be applied in clinical practice for patients

who are identified to have gram-negative bacteremia. In the first scenario, patient A is a 10-year-old with congenital renal anomalies who experienced a urinary tract infection caused by *E. coli* resistant to cefepime within the past 6 months and received treatment with piperacillin-tazobactam. The decision tree algorithm would categorize this patient as being at high risk of a BSA-resistant infection, and this patient may warrant broader empiric antibiotic therapy. In the second scenario, patient B is a 2-year-old receiving chemotherapy via central catheter for a hematologic malignancy, has never been treated with a carbapenem, but has had 2 prior episodes of gram-negative bloodstream infections sensitive to cefepime and piperacillin-tazobactam. This patient would be considered at lower risk of BSA-resistant infection, and it may be reasonable to empirically treat with cefepime or piperacillin-tazobactam.

Few studies have reported the longitudinal pattern of gram-negative resistance in patients with repeated infections [35–37]. We found that a patient might have varying resistance phenotypes from one episode to another; however, we did not examine the details of possible isolate relatedness over time. As expected, more patients with prior BSA-resistant episodes than with prior nonresistant episodes had subsequent resistant episodes. Our regression model demonstrated a 7% increased odds of infection owing to a BSA-resistant organism with each additional episode of bacteremia. These findings are consistent with

a study by Agarwal and Larson [36], who found that patients had a 13% greater risk of developing an MDRGN infection with each additional infectious episode. These findings support the idea that cumulative infection history increases a patient's risk of a subsequent resistant infection. Future studies examining the evolution within a patient of antibiotic susceptibility changes over time may be helpful to determine whether resistance is related to antibiotic exposure, acquisition of new bacteria strains, or transfer of genetic elements between strains.

There are several limitations to our study. It was retrospective and did not include outpatient data. This could lead to possible misclassification or missing data, although we would expect the effect to be similar by resistance status. There may have been bloodstream infections that we did not capture if the patients initially presented and had blood cultures obtained at an outside facility. CHP is the only tertiary care pediatric facility serving Western Pennsylvania, so most complex cases in the region are managed at this hospital. There may be additional risk factors associated with BSA-resistant bloodstream infection that we did not capture. The included variables were selected owing to their practical utility, because they should be available to clinicians through patient interview or brief medical chart review. Future analyses should examine whether additional patient characteristics or variables captured using an alternative approach may improve the sensitivity of the prediction algorithm.

Because the current study specifically evaluated BSA resistance in bloodstream infections, the findings may not be generalizable to other types of infections or colonization status. Ideally, it would have been possible to distinguish cefepime and/or piperacillin-tazobactam resistance from carbapenem resistance, using a staged approach, because this would be clinically relevant. For example, if a patient had a high risk of CPT resistance, then a second tree would be applied to determine whether he or she had an isolate with a high likelihood of carbapenem resistance. Given the limited number of carbapenem-resistant infections in our cohort, we were unable to develop such a 2-step approach. Larger cohorts are needed to develop reliable prediction models for this additional ability to distinguish CPT and carbapenem resistance. Finally, the data set was used to both develop and validate the decision tree. Although we performed leave-one-out cross-validation, the tree may perform differently in a different cohort of patients. The constructed tree needs to be validated in diverse patient populations before incorporation into clinical practice.

In conclusion, we developed a decision tree to provide individualized risk assessment of resistance to BSAs of cefepime, piperacillin-tazobactam, or carbapenems to assist with empiric antibiotic selection for children with gram-negative bloodstream infections. The constructed tree needs to be validated more broadly before incorporation into clinical practice but offers a novel approach for risk assignment. This study highlights the importance of considering patients' recent antibiotic

treatment history and prior culture results when assessing empiric antibiotic treatment. Future studies are needed to refine prediction algorithms for individual patients' risk of antibiotic resistance and assess the potential impact on patient management. Decision trees have the potential to be valuable tools that can assist with patient-specific, evidence-based recommendations to optimize antibiotic treatment decisions.

Notes

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