ORIGINAL ARTICLE

A New Metric of Antibiotic Class Resistance in Gram-Negative Bacilli Isolated from Hospitalized Children

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OBJECTIVE. The purpose of this study was to describe patterns of infection or colonization with antibiotic-resistant gram-negative bacilli (GNB) in hospitalized children utilizing an electronic health record.

SETTING. Tertiary care facility.

PARTICIPANTS. Pediatric patients 18 years of age or younger hospitalized from January 1, 2006, to December 31, 2008.

METHODS. Children were identified who had (1) at least 1 positive culture for a multidrug-resistant (MDR) GNB, defined as a GNB with resistance to 3 or more antibiotic classes; or (2) additive drug resistance, defined as isolation of more than 1 GNB that collectively as a group demonstrated resistance to 3 or more antibiotic classes over the study period. Differences in clinical characteristics between the 2 groups were ascertained, including history of admissions and transfers, comorbid conditions, receipt of procedures, and antibiotic exposure.

RESULTS. Of 56,235 pediatric patients, 46 children were infected or colonized with an MDR GNB, of which 16 were resistant to 3 classes and 30 were resistant to 4 classes. Another 39 patients had positive cultures for GNB that exhibited additive drug resistance. Patients with additive drug resistance were more likely than patients with MDR GNB to have had previous admissions to a long-term facility (8 vs 2; $P = .04$) and had more mean admissions (7 vs 3; $P < .01$) and more mean antibiotic-days ($P < .01$ to $P = .02$). Six patients with additive drug resistance later had a positive culture with an MDR GNB.

CONCLUSIONS. An electronic health record can be used to track antibiotic class resistance in GNB isolated from hospitalized children over multiple cultures and hospitalizations.

Infect Control Hosp Epidemiol 2012;33(6):602-607

According to the National Healthcare Safety Network, the prevalence of multidrug resistance among gram-negative bacilli (GNB) has been increasing.[1] While the exact definitions for multidrug-resistant (MDR) GNB vary,[2] these organisms are especially concerning since they may be susceptible to only a single antibiotic class. Risk factors for infections with MDR GNB in children include prior hospitalization, admission to intensive care units (ICUs) and chronic care facilities, prolonged length of stay, receipt of mechanical ventilation, vascular catheterization, and antibiotic exposure.[3-7]

Some hospitalized children, while not developing infections caused by GNB with multidrug resistance, may nevertheless be infected or colonized with multiple GNB that each exhibit 1 or 2 antibiotic class resistance. It is possible that these children may develop infections with GNB over time that collectively exhibit resistance to multiple antibiotic classes. For chronically ill children, these infections may occur over multiple hospital admissions. They may be at subsequent risk of developing infections with MDR GNB, since GNB may share resistance genes via mechanisms such as conjugation or transduction.[8]

The purpose of this study was to utilize an electronic health record to describe patterns of antibiotic class resistance of GNB isolated from hospitalized children's clinical cultures. We identified pediatric patients who had (1) a positive culture for an MDR GNB, defined as a GNB with resistance to 3 or more antibiotic classes; and (2) additive drug resistance, defined as isolation of more than 1 GNB that collectively as a group of GNB over the study period demonstrated resistance to 3 or more antibiotic classes. We developed this novel definition to describe patients who had cultures from which no MDR GNB were isolated but had several different GNB that, as a group, were resistant to 3 of more antibiotic classes. Our goal was to describe a burden of resistance across multiple cultures and species, beyond definitions of MDR GNB. We used the electronic health record to compare clinical characteristics between each group of patients. Finally, we evaluated whether the electronic health record could be used to

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Received November 12, 2011; accepted January 22, 2012; electronically published April 13, 2012.
 0899-823X/2012/3306-0010$15.00. DOI: 10.1086/665709

assess whether patients with additive drug resistance develop subsequent infection or colonization with MDR GNB.

METHODS

Study Setting

This study was conducted at the 4 hospitals of the NewYork-Presbyterian healthcare system, located in New York City. NewYork-Presbyterian is the largest hospital system in New York State, serving the local communities of northern and eastern Manhattan, and is a referral center for the New York–New Jersey–Connecticut tristate area. NewYork-Presbyterian is affiliated with the medical schools of Cornell and Columbia University. The majority of children are admitted to 1 of 2 pediatric acute tertiary care facilities, which have 291 hospital beds combined. Approximately 3,500 surgeries are performed on children each year. NewYork-Presbyterian has 6 pediatric ICUs, including surgical, medical, and neonatal ICUs.

Study Subjects

Study subjects were patients 18 years of age or younger who were hospitalized at NewYork-Presbyterian from January 1, 2006, to December 31, 2008. Patients seen only in the emergency department or in ambulatory clinics were not included.

Data Source

The study data were originally obtained for a parent study measuring the distribution of costs of antimicrobial-resistant infections (National Institutes of Health grant R01 NR010822). Data were retrospectively extracted from the clinical data warehouse of the NewYork-Presbyterian system, which integrates data from more than 20 clinical electronic sources, including microbiology laboratory, pharmacy, and administrative records. A description of the development and architecture of the database has been published elsewhere.[9] For each patient, data from all hospital admissions during the study period were included. All patient information was deidentified and linked to a randomly generated study identification number. Institutional review board approval was obtained from the Columbia University Institutional Review Board.

Study Outcomes

For all patients in the database, we extracted results of bacterial cultures from all body sites with growth for common epidemiologically and clinically significant GNB, including antimicrobial susceptibility testing results (Table 1).

For our study purposes, antibiotic class resistance was defined as a qualitative minimum inhibitory concentration interpretation of resistant, intermediate, or not reported to all antibiotics in a class. We chose this broader definition of resistance to reflect the antibiotic choices available to the clinician, since agents with intermediate activity may not achieve sufficient tissue concentration for effective therapy. Antibiotic classes were defined as β-lactams, aminoglycosides, fluoroquinolones, and carbapenems. Carbapenem antibiotics were categorized separately from other β-lactam agents because of their broad spectrum of activity against many MDR GNB. Aztreonam, a monobactam agent, was categorized with β-lactam antibiotics.

We defined 2 outcomes using the extracted microbiological data: (1) positive culture for an MDR GNB and (2) positive cultures that exhibited additive drug resistance. An MDR GNB was defined as a GNB with resistance to 3 or more antibiotic classes. The date of the MDR outcome was defined as the collection date of the first culture from which the MDR organism was isolated. Additive drug resistance was defined as isolation of more than 1 GNB that additively demonstrated resistance to 3 or more antibiotic classes at least once during the study period, without having a previous MDR GNB infection. By definition, cultures contributing to additive drug

TABLE 1. Gram-Negative Bacilli (GNB) and Routine Antimicrobial Susceptibility Testing Performed

Organism	β-lactams	Aminoglycoside	Fluoroquinolones	Carbapenems
Pseudomonas spp.	Cefazolin	Gentamicin	Ciprofloxacin	Meropenem
Klebsiella spp.	Cefuroxime	Tobramycin	Levofloxacin	Imipenem
Acinetobacter spp.	Cefoxitin	Amikacin		
Escherichia coli	Cefotetan			
Proteus spp.	Cefotaxime			
Enterobacter spp.	Ceftriaxone			
Serratia spp.	Ceftazidime			
Miscellaneous[a]	Cefipime			
	Ampicillin sulbactam			
	Piperacillin			
	Piperacillin tazobactam			
	Aztreonam			

NOTE. Slight variations may have occurred in antimicrobial susceptibility testing, depending on individual species and/or clinician request.

[a] Includes *Morganella*, *Citrobacter*, *Aeromonas*, and nonidentified GNB.

resistance were collected over more than 1 date and included GNB of 1 species (with different antibiograms for each isolate) or different species. The date of the additive drug resistance outcome was defined as the first date that the patient developed additive drug resistance (i.e., the first point in time that the patient's cultures for GNB exhibited additive resistance to 3 or more antibiotics). For each patient, cumulative hospitalization days between first admission and the development of the study outcomes were calculated. Because patients could potentially have both an MDR GNB and additive drug resistance, they were classified by which event occurred first.

During the study period, both microbiological laboratories of NewYork-Presbyterian used the Vitek 2 system (AB bioMerieux) as the primary method for antimicrobial susceptibility testing of GNB. The antimicrobial susceptibility testing performed for each species of GNB is provided in Table 1. Our study was performed before the recommendation by the Clinical Laboratory Standards Institute in 2010 to lower minimum inhibitory concentration breakpoints for cephalosporins and aztreonam.[10]

Clinical Characteristics

For each of the outcomes, we ascertained the presence of clinical characteristics before the development of MDR or additive drug resistance for all patients admitted during the study period. Data collected included age, sex, number of admissions, admission source, number of hospital transfers from other institutions, transfer from a chronic care facility, cumulative hospitalization days, cumulative ICU hospitalization days, and admission to a neonatal ICU. The following comorbid conditions were documented by determining the presence of any related *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes for principal and secondary diagnoses on admission(s): cystic fibrosis, short bowel syndrome, malignancy, solid organ or bone marrow transplant, and burns. Procedure-based clinical characteristics included duration of central venous catheter and urinary catheter placement, receipt of mechanical ventilation, and surgical procedures. Antimicrobial exposure was calculated as days of therapy for each of 4 classes of antibiotics (β-lactams, aminoglycosides, fluoroquinolones, and carbapenems). A day of therapy was defined as a receipt of 1 or more doses of an antibiotic from a class on a calendar day. If different antibiotics of the same class were given on a calendar day, only 1 day of therapy was recorded.

Statistical Analyses

Frequencies and percentages were calculated for categorical variables, and medians and ranges were calculated for continuous variables. The distribution of clinical characteristics between the study outcomes were compared using χ^2 tests, Fisher exact tests, and t tests. All statistical analyses were completed in SAS 9.2 for Windows (SAS Institute).

RESULTS

From January 1, 2006, to December 31, 2008, 56,235 patients 18 years of age or younger were admitted to NewYork-Presbyterian, accounting for 68,280 admissions. The median age was 34 months. The median cumulative length of stay during the study period was 3 days (range, 1–609 days). Overall, 50,346 (90%) of patients had only 1 hospitalization during the study period, 721 (1%) patients had more than 5 admissions, and 172 (0.31%) patients had more than 10 admissions.

The number of patients with at least 1 culture with growth for GNB with resistance to β-lactam, aminogylcosides, fluoroquinolones, or carbapenem antibiotics was 147 (0.26%), 111 (0.20%), 241 (0.43%), and 222 (0.39%) respectively. The number of patients with GNB with resistance to 1, 2, 3, and 4 antibiotic classes were 232 (0.41%), 56 (0.10%), 37 (0.07%), and 48 (0.09%), respectively.

Forty-six patients (0.08%) had infection or colonization with an MDR GNB, of which 16 were resistant to 3 classes and 30 were resistant to 4 classes of antibiotics. *Klebsiella* spp. ($n = 10$), *Pseudomonas* spp. ($n = 14$), and *Acinetobacter baumanii* ($n = 13$) accounted for 80% of the MDR GNB.

An additional 39 (0.07%) children had positive cultures for GNB that exhibited additive drug resistance. Ninety isolates contributed to additive drug resistance, of which *Klebsiella* spp. ($n = 18$), *Pseudomonas* spp. ($n = 31$), and *A. baumanii* for each outcome is provided in Table 2. While both MDR and additive drug resistance were isolated from a number of body sites, respiratory cultures were the most common source, accounting for 46% (21/46) and 51% (46/90) of the cultures for MDR and additive drug resistance patients, respectively. Additive drug resistance was significantly more likely to be isolated from blood than MDR (15.6% [14/90] and 4.3% [2/46], respectively; $P < .04$). The incidence rate for MDR GNB and additive drug resistance was 1.19 and 1.01 per 1,000 hospital-days, respectively. Table 3 describes the body sites from which GNB were isolated for patients with MDR GNB and additive drug resistance.

Of the 39 patients with additive drug resistance, 11 patients

TABLE 2. Organisms Isolated from Patients with Multidrug-Resistant (MDR) Gram-Negative Bacilli (GNB) and Additive Drug Resistance

Organism	MDR GNB	Additive drug resistance
Pseudomonas	14 (30)	31 (34)
Klebsiella	10 (22)	18 (20)
Acinetobacter	13 (28)	11 (12)
Escherichia coli	5 (11)	11 (12)
Proteus	0 (0)	5 (6)
Enterobacter	1 (2)	6 (7)
Serratia	1 (2)	3 (3)
Miscellaneous	2 (4)	5 (6)
Total	46 (100)	90 (100)

NOTE. Data are no. of isolates (%).

https://doi.org/10.1086/665709 Published online by Cambridge University Press

TABLE 3. Culture Sources of Gram-Negative Bacilli (GNB) of Patients with Multidrug-Resistant (MDR) GNB and Additive Drug Resistance

Body site	MDR GNB	Additive drug resistance
Blood	2	14
Urine	8	16
Respiratory tract	21	46
Wound	6	10
Gastrointestinal tract/stool	5	3
Miscellaneous	4	1
Total	46	90

NOTE. Data are no. of isolates (%).

had 1 species over 2 or more dates contributing to additive drug resistance. Twenty-one patients had 2 unique species, and 7 patients had 3 unique species. The time between clinical cultures ranged from 0 to 316 days. Twenty-nine patients had additive drug resistance from cultures obtained during a single hospital admission, while 10 patients had additive drug resistance from cultures obtained across 2 or more admissions.

We compared clinical characteristics between hospitalized children with MDR GNB and those with additive drug resistance (Table 4). Patients with additive drug resistance were more likely to have had previous admission to a long-term facility (8 vs 2; $P = .04$). Mean number of admissions (7 vs 3; $P < .01$), ICU days (53 vs 23; $P = .03$), and central venous catheter days (31 vs 12; $P = .01$) were higher among patients with additive drug resistance than patients with MDR GNB. Similarly, the mean days of therapy for all classes of antibiotics was higher among patients with additive drug resistance than those patients with MDR GNB. The difference in mean cumulative hospitalized time between the 2 groups was not significant (92.6 vs 86 days; $P = .06$).

Of the patients with additive drug resistance, 6/39 (15%) developed subsequent infection or colonization with an MDR GNB before the end of the study period. Five patients had MDR GNB within the same admission, and 1 had an MDR GNB on the subsequent admission. The time between study date of additive drug resistance and first MDR infection or colonization ranged from 2 to 563 days, of which 5 occurred within the same admission All of the 6 MDR positive cultures included at least 1 species that earlier contributed to additive drug resistance.

DISCUSSION

To the best of our knowledge, our study is the first to use a metric of additive antibiotic class resistance to describe GNB isolated from hospitalized children. At our hospital, a small proportion of children had clinical cultures with growth for MDR GNB. Similarly, a small but comparable number of children had additive drug resistance. We found clinical differences between these patients, particularly with regard to antibiotic exposure, previous hospital admissions, and transfers from a long-term care facility. Last, we showed that some children with additive drug resistance subsequently developed infection or colonization with an MDR GNB.

For both MDR and additive drug resistance patients, *Klebsiella*, *Acinetobacter*, and *Pseudomonas* spp. were the most commonly isolated organisms with antibiotic class resistance. Comparisons of prevalence with other institutions and regions are difficult, since definitions for multidrug resistance vary.[2] Nonetheless, these species carry a high burden of antibiotic resistance. From 2006 to 2008, the National Healthcare Safety Network reported that up to 60% of *A. baumanii*, 15% of *Klebsiella pneumoniae*, and 10% of *Pseudomonas aeruginosa* were MDR, defined as resistance to all agents from 3 or more antibiotic classes.[1]

Six patients in this study had additive drug resistance before developing a positive culture with MDR GNB. Patients with unrecognized carbapenem-resistant *K. pneumoniae* colonization have served as reservoirs for transmission during healthcare-associated outbreaks.[11] In tertiary care settings and chronic care facilities, where chronically ill children can have multiple hospital admissions, a metric of additive antibiotic resistance can be useful to track patients who have the potential to harbor and transmit antibiotic-resistant organisms. For example, determining additive drug resistance status of patients could be used to augment surveillance strategies for carbapenem-resistant Enterobacteriaceae, as recommended by the Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention, such as periodic review of microbiological records and point prevalence surveys.[12]

Our study methodology relied on an electronic health record system that integrated information from administrative, clinical, and microbiological data sources. Our hospital has an internally developed microbiology-based detection system to identify and track patients with epidemiologically significant organisms, including MDR GNB, in real time. Automated systems such as these have been shown to reliably identify antimicrobial susceptibility patterns in spatial or temporal clusters that would suggest clonality and a common source.[13] In addition, automated systems have been shown to augment active surveillance efforts. For example, using an electronic health record to document antibiotic exposure in the past year, Morgan et al[14] developed a prediction rule to identify most patients with methicillin-resistant *Staphylococcus aureus* and nearly all patients with vancomycin-resistant enterococci colonization while culturing 49% fewer patients. While not replacing existing surveillance methods, incorporation of history of antibiotic class resistance into automated surveillance systems may identify patients with additive drug resistance on admission and potentially those colonized with MDR organisms. Knowledge of additive drug resistance may also help guide empiric antibiotic therapy for a patient's previous microbiology results and known antibiotic resistance among GNB.

We were surprised to note that patients with additive drug

TABLE 4. Comparison of Clinical Characteristics between Patients with Multidrug-Resistant (MDR) Gram-Negative Bacilli (GNB) and Additive Drug Resistance

Variable	MDR GNB ($n = 46$)	Additive drug resistance ($n = 39$)	P
Admission data			
Age, months	68	56	.49
Sex, male	29	19	.20
No. of admissions	3	7	<.01
No. of transfers	0.5	1	.04
Cumulative hospitalization, days	86	92.6	.06
Cumulative ICU stay, days	23	53	.03
Admission to neonatal ICU	1	1	1.00
Transfer from long-term care facility	2	8	.04
Diagnoses			
Cystic fibrosis	1	4	.17
Short bowel syndrome	2	6	.13
Malignancy	6	3	.50
Transplant	2	4	.41
Burn	7	1	.06
Procedures			
Surgical procedure	30	26	1.00
Mechanical ventilation	32	28	1.00
Central venous catheter, days	12	31	.01
Urinary catheter, days	12	20	.12
Antibiotic days of therapy			
β-lactams	6	22	<.01
Aminogylcosides	2	13	<.01
Fluoroquinolones	1	6	.01
Carbapenems	1	10	.02

NOTE. P values from χ^2 test, t test, or Fisher exact test. ICU, intensive care unit.

resistance were more likely to receive days of therapy for all 4 classes of antibiotics. They also had more hospital admissions, transfers, and days of hospitalization in an ICU and were more likely to have had a stay at a long-term care facility. The differences in clinical characteristics we observed between patients with MDR and additive drug resistance may reflect differences in antibiotic selective pressure and exogenous acquisition via healthcare workers, other patients, or the environment.[15-17] For example, patients with additive drug resistance may be more likely to have chronic medical conditions (evidenced by more admissions, transfers, and stays at long-term care facilities) requiring antibiotics, thus experiencing more selective pressure. Interhospital transmission of antibiotic class resistant GNB may be a factor, demonstrated previously for carbapenem-resistant *Acinetobacter* in New York City.[18] Unfortunately, small sample size precluded measurement of the independent effects of each of the variables.

Our study had several limitations. We included all positive cultures for GNB and therefore could not distinguish between infection and colonization. Our definition for MDR and additive drug resistance organisms included intermediate and missing testing and therefore may have overestimated resistance prevalence compared with other definitions of MDR. We did not perform screening cultures for resistant GNB on first admission, nor did we have data from outpatient care (such as antibiotic exposure) or hospitalizations at other institutions. Determination of clinical diagnoses by *ICD-9-CM* codes may have limited sensitivity.[19] Because of censoring, there may have been limitations in the measurement of clinical characteristics between patients who have MDR GNB and those with additive drug resistance. Nonetheless, because the mean in hospital observation time was nearly identical, our findings suggest clinical differences between the 2 groups. The majority of children in our study had only 1 hospital admission and therefore may have limited opportunities to be cultured and acquire additive drug resistance.

Despite these limitations, our study demonstrates that a metric of additive antibiotic resistance for GNB can be developed using electronic health record data. Furthermore, this metric could be used to identify a pool of patients that may harbor MDR organisms. In tertiary care, where hospitalized children may transition between multiple providers and institutions, additional strategies to efficiently and rapidly detect and control resistant GNB are needed.

ACKNOWLEDGMENTS

Financial support. Funding was provided by the National Institute of Nursing Research (R01 NR010822). We acknowledge support provided by the Center for Interdisciplinary Research to Reduce Antimicrobial Resistance at

the School of Nursing, Columbia University. S.J.P. acknowledges grant support (KL2 RR024157) from the Irving Institute for Clinical and Translational Research at Columbia University.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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