ORIGINAL ARTICLE

Pediatric Antimicrobial Susceptibility Trends across the United States

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OBJECTIVE.   Antimicrobial susceptibility patterns across US pediatric healthcare institutions are unknown. A national pooled pediatric antibiogram (1) identifies nationwide trends in antimicrobial resistance, (2) allows across-hospital benchmarking, and (3) provides guidance for empirical antimicrobial regimens for institutions unable to generate pediatric antibiograms.

METHODS.   In January 2012, a request for submission of pediatric antibiograms between 2005 and 2011 was sent to 233 US hospitals. A summary antibiogram was compiled from participating institutions to generate proportions of antimicrobial susceptibility. Temporal and regional comparisons were evaluated using χ^2 tests and logistic regression, respectively.

RESULTS.   Of 200 institutions (85%) responding to our survey, 78 (39%) reported generating pediatric antibiograms, and 55 (71%) submitted antibiograms. Carbapenems had the highest activity against the majority of gram-negative organisms tested, but no antibiotic had more than 90% activity against *Pseudomonas aeruginosa*. Approximately 50% of all *Staphylococcus aureus* isolates were methicillin resistant. Western hospitals had significantly lower proportions of *S. aureus* that were methicillin resistant compared with all other regions tested. Overall, 21% of *S. aureus* isolates had resistance to clindamycin. Among *Enterococcus faecium* isolates, the prevalence of susceptibility to ampicillin (25%) and vancomycin (45%) was low but improved over time ($P < .01$), and 8% of *E. faecium* isolates were resistant to linezolid. Southern hospitals reported significantly higher prevalence of *E. faecium* with susceptibilities to ampicillin, vancomycin, and linezolid compared with the other 3 regions ($P < .01$).

CONCLUSIONS.   A pooled, pediatric antibiogram can identify nationwide antimicrobial resistance patterns for common pathogens and might serve as a useful tool for benchmarking resistance and informing national prescribing guidelines for children.

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Outcomes of patients with infections are optimized when early treatment with an appropriate antimicrobial regimen is selected, which occurs most often when there is knowledge of antimicrobial susceptibility patterns.[1-4] In the adult population, achieving a high rate of appropriate empirical antibiotic therapy has become increasingly challenging because of the rise of antibiotic-resistant pathogens.[5] To date, antimicrobial susceptibility patterns across US pediatric healthcare institutions over time and in various geographical locations have not been evaluated, and existing single-center studies suggest pediatric data differ from adult data.[6,7]

Antibiograms summarize institutional patterns of antimicrobial susceptibilities.[8] They can be informative tools to monitor antimicrobial resistance trends within an institution and are equally important for guiding informed decisions about empirical antibiotic therapy.[6,9] Although many institutions generate antibiograms, a national pooled antibiogram for children does not exist. Pooling antibiograms from a sampling of US pediatric hospitals could (1) identify nationwide

patterns in antimicrobial resistance, (2) allow across-hospital benchmarking, and (3) provide useful data to guide empirical antimicrobial therapy for under-resourced institutions that are unable to generate antibiograms. Because active, population-based surveillance can be time consuming and resource intensive, aggregated antibiograms may be a reasonable alternative. Consolidated antibiograms have been compiled successfully in the past by state health departments and the Veterans Affairs System.[10-12] The objectives of this study were to identify antibiotic susceptibility patterns among hospitalized children in the United States and to evaluate regional and temporal differences in susceptibility data using available pediatric antibiograms.

METHODS

Data Collection

In January 2012, a survey and request for submission of pediatric antibiograms between 2005 and 2011 was sent to (1)
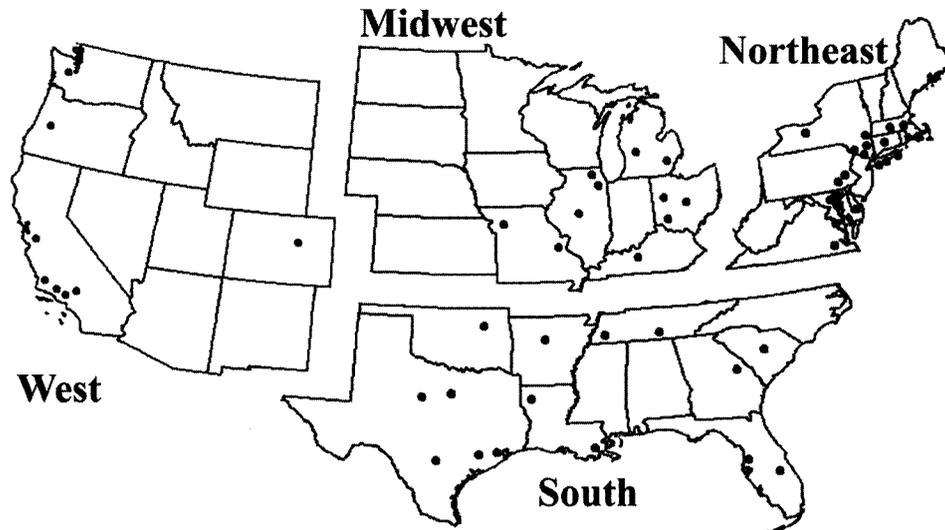
PEDIATRIC ANTIBIOGRAMS 1245

FIGURE 1.   Map of the United States divided into census regions. Each dot represents an institution that contributed pediatric antibiograms.

all members of the Society for Healthcare Epidemiology of America Research Network, (2) all Pediatric Infectious Diseases Society members, and (3) all institutions (not captured through the above mechanisms) with pediatric residency programs identified through the American Medical Association. A total of 233 institutions caring for children were contacted.

Institutions were asked to complete a 15-question web-based survey (http://www.surveymonkey.com) regarding the demographic characteristics of their institutions and the methods used for generation of their antibiograms. Compliance with 6 major Clinical and Laboratory Standards Institute (CLSI) recommendations were evaluated, including (1) reporting data at least annually, (2) exclusion of duplicate isolates, (3) exclusion of surveillance isolates, (4) requiring at least 30 isolates for each reported species, (5) separation of unit-specific data, and (6) separation of urine and nonurine isolates.[13]

Statistical Analysis

A national antibiogram was generated using data from participating institutions across the United States. Data for clinically important gram-positive and gram-negative organisms from a 24-month period (January 2010–December 2011) were included. Similarly, region-specific pediatric antibiograms were generated for the Northeast, Midwest, South, and West (according to US census classifications), focusing on a few preselected organism (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterococcus faecium*) and drug combinations.[14] For institutions with separate antibiograms for special populations, such as intensive care unit patients, patients with cystic fibrosis, or outpatients, all available antibiograms for a given year for the institution were combined to develop a composite antibiogram for that institution to allow for comparability across institutions. Sim-

ilarly, because the majority of institutions did not separately report data by source (eg, urine), all sources were consolidated into a single antibiogram for each institution. Any hospital that included duplicate isolates in generating their antibiograms was excluded from additional analysis. To evaluate trends over time, susceptibility data from 2010–2011 were compared with data from 2005–2006. Only institutions that provided data from both periods were included in this analysis. Antibiotic-organism susceptibility proportions over time were analyzed using χ^2 testing. Because it was anticipated that some institutions may have incorporated the January 2010 CLSI recommendations to lower breakpoints from less than or equal to 8 μg/mL to less than or equal to 1 μg/mL against Enterobacteriaceae, a sensitivity analysis was conducted that removed institutions that adhered to the 2010 recommendations to determine whether that unduly impacted susceptibility trends for Enterobacteriaceae between 2005 and 2011.

Simple logistic regression models were created for each bacteria-antibiotic combination, with region as the independent variable, the proportion susceptible as the dependent variable, and institutions in the northeastern region as the reference group. Logistic regression was performed using PROC GENMOD and specifying for type 3 analyses, which examined whether region is a predictor of susceptibility. A 2-sided P value of less than .05 was considered significant for all analyses. Data were entered into Microsoft Excel. Statistical analyses were performed using SAS, version 9.2 (SAS Institute).

RESULTS

Survey Response

Of the 233 institutions that were contacted, 200 (85%) responded to our survey. Seventy-eight (39%) of the 200 in-

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TABLE 1. Pooled Proportions of Antibiotic Susceptibility Data for Gram-Negative Organisms from 2010–2011 Pediatric Antibiograms among 55 Participating Institutions across the United States

	Susceptible isolates, % (no. of isolates tested)								
Pathogen	Ampicillin-sulbactam	Ceftriaxone	Cefepime	Piperacillin-tazobactam	Meropenem/imipenem	Aztreonam	Ciprofloxacin	Gentamicin	Amikacin
Escherichia coli	58.6 (27,814)	96.4 (39,591)	98.4 (40,595)	96.1 (46,805)	99.6 (43,277)	95.8 (13,734)	89.7 (45,025)	92.6 (50,774)	99.0 (41,321)
Klebsiella pneumoniae	83.0 (8,119)	94.2 (10,210)	95.4 (8,920)	93.3 (10,883)	98.4 (9,992)	94.7 (3,553)	94.5 (6,452)	93.3 (11,415)	98.1 (10,418)
Enterobacter cloacae	19.1 (2,844)	77.7 (4,594)	96.1 (5,621)	80.4 (6,099)	97.9 (6,244)	77.7 (2,917)	95.6 (6,096)	95.0 (6,859)	98.7 (6,077)
Citrobacter freundii	38.7 (1,691)	81.2 (1,923)	96.4 (1,900)	80.9 (1,945)	99.6 (2,056)	85.1 (1,281)	92.2 (2,075)	88.1 (2,235)	97.9 (1,180)
Serratia marcescens	3.8 (1,902)	95.3 (4,238)	98.8 (3,811)	92.1 (5,225)	98.3 (5,226)	94.6 (1,807)	93.8 (5,059)	88.9 (4,580)	97.7 (3,058)
Pseudomonas aeruginosa	...	...	83.5 (15,876)	89.5 (18,174)	88.5 (18,400)	66.4 (9,754)	85.0 (17,526)	74.8 (19,915)	88.9 (16,368)

stitutions reported generating pediatric antibiograms. Antibiograms were submitted from 55 of the 78 institutions, with the distribution of sites by region displayed in Figure 1. Approximately 45% of responding hospitals had more than 200 pediatric beds, 33% had 101–200 beds, 11% had 51–100 beds, and 11% had fewer than 50 pediatric beds. There was no significant difference between distribution of bed sizes across regions.

Of the 55 centers submitting antibiograms, the majority adhered to CLSI recommendations to update antibiograms at least annually (91%), eliminate duplicate cultures (91%), and exclude surveillance cultures (91%), such as nasal or perirectal swab samples to screen patients for carriage of methicillin-resistant *S. aureus* or vancomycin-resistant *Enterococcus* species, respectively. The minority of institutions, however, required at least 30 isolates for each organism-antibiotic combination (16% of institutions); reported the preparation of unit-based antibiograms for the neonatal intensive care unit, pediatric intensive care unit, or both (38%); or reported separate antibiograms for urine isolates (38%), outpatients (27%), or patients with cystic fibrosis (31%). Only 16% of centers complied with all 6 CLSI recommendations for generation of antibiograms. January 2010 CLSI recommendations to lower third-generation cephalosporin susceptibility breakpoints were represented in only 24% of 2010–2011 antibiotics; a sensitivity analysis that removed these institutions did not alter results, as described below.

Gram-Negative Antibiotic Susceptibility Data

Mean antibiotic susceptibility for select clinically relevant gram-negative organisms for 2010–2011 and the total number of isolates contributing to the analysis are shown in Table 1. In general, most antibiotics were highly active against the majority of organisms tested, with some notable exceptions. Ampicillin-sulbactam activity against common gram-negative enteric pathogens was inferior to that of most other β-lactams; 59% and 83% activity against *Escherichia coli* and *K. pneumoniae*, respectively; however, susceptibility of both of these organisms to ampicillin-sulbactam significantly improved between 2005 and 2011 (P < .01). Susceptibility to ampicillin-sulbactam was low (4%–39%) for organisms generally indicative of previous healthcare exposure, namely *En-*

terobacter species, *Citrobacter freundii*, and *Serratia marcescens*. Twenty-two percent of *Enterobacter cloacae* isolates were resistant to ceftriaxone, a resistance pattern thought to be a proxy for hyperproduction of inducible chromosomally mediated AmpC β-lactamases.[15] Six sites reported specific extended-spectrum β-lactamase (ESBL) testing results for *E. coli* and *K. pneumoniae* in 2010–2011, and ESBL production was described in 8% of all *E. coli* and 6% of all *K. pneumoniae* isolates from sources other than urine. As anticipated, meropenem and imipenem had the highest activity against the majority of gram-negative organisms tested.

Cefepime retained significantly higher activity compared with piperacillin-tazobactam against *E. cloacae*, *C. freundii*, and *Serratia marcescens* (P < .01), although *P. aeruginosa* was more susceptible to piperacillin-tazobactam than cefepime (90% vs 84%; P < .01). Of note, none of the participating institutions had incorporated the June 2011 CLSI recommendation to lower the piperacillin-tazobactam minimum inhibitory concentration against *Pseudomonas* species from less than or equal to 64 µg/mL to less than or equal to 16 µg/mL in their 2011 antibiograms. *P. aeruginosa* susceptibility to aztreonam was only 66%, which was inferior to all β-lactams tested. Although susceptibility to aminoglycosides, β-lactams, and fluoroquinolones remained relatively unchanged from 2005 to 2011, *P. aeruginosa* susceptibility to aztreonam significantly decreased from 75% to 66% (P < .01). No more than 90% of *P. aeruginosa* isolates were susceptible to any antibiotic agent.

Gram-Positive Antibiotic Susceptibility Data

Antibiotic susceptibility data for *S. aureus*, *Enterococcus faecalis*, and *E. faecium* for select agents are shown in Table 2. Approximately 50% of tested isolates of *S. aureus* were methicillin resistant. Overall susceptibility of *S. aureus* to clindamycin was 79%. No *S. aureus* isolates were resistant to vancomycin. Trimethoprim-sulfamethoxazole and tetracycline remained highly active against *S. aureus* across the United States. Ampicillin displayed excellent activity against *E. faecalis* (>99%) but poor activity against *E. faecium* (25%). Of concern, nearly 8% of *E. faecium* isolates were not susceptible to linezolid. Susceptibility of *E. faecium* to ampicillin and vancomycin improved significantly over time (P < .01; Fig. 2).

TABLE 2. Pooled Proportions of Antibiotic Susceptibility Data for Gram-Positive Organisms from 2010–2011 Pediatric Antibiograms among 55 Participating Institutions across the United States

| Pathogen | Susceptible isolates, % (no. of isolates tested) | | | | | | |
	Ampicillin	Oxacillin	Clindamycin	Trimethoprim-sulfamethoxazole	Tetracycline	Vancomycin	Linezolid
Staphylococcus aureus	...	50.5 (73041)	78.8 (84027)	97.6 (85642)	95.3 (40765)	100.0 (85684)	99.9 (59304)
Enterococcus faecalis	99.7 (6775)	...	...	...	...	99.7 (7588)	97.6 (6137)
Enterococcus faecium	24.8 (1181)	...	...	...	...	44.6 (1124)	92.5 (1104)

Regional Resistance Trends

Regional antibiotic susceptibility trends for *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, and *E. faecium* are shown in Figure 3. Although scattered differences in susceptibilities of gram-negative organisms were seen, no patterns were noted. Western hospitals had significantly higher proportions of *S. aureus* that were methicillin susceptible (66%) compared with all other regions tested ($P < .01$). Southern hospitals reported *E. faecium* with significantly higher susceptibilities to ampicillin, vancomycin, and linezolid compared with the other regions ($P < .01$).

DISCUSSION

By creating a pooled pediatric antibiogram, we have taken a step toward estimating the profile of national antibiotic susceptibility patterns for children. Our results demonstrate that antibiotic susceptibility trends for children in the United States have remained relatively stable for the majority of tested organisms over a 7-year period. Although this is reassuring, this must be considered in the context of the limited number of new antimicrobial agents available in the drug-development pipelines and the increasing prevalence of drug resistant infection among adults.[16] Unless we are judicious with our use of antibiotics in children, we may encounter a resistance scenario similar to what is occurring in the adult population.[5]

Antibiograms serve several useful functions. They can be informative of local resistance patterns, guide empirical antibiotic therapy choices, identify opportunities to reduce inappropriate use of antibiotics, and help target infection prevention and control practices.[17-19] There is currently no uniform system in place for evaluating national pediatric drug resistance trends, and active population-based surveillance can be both resource intensive and time consuming. Because a number of institutions already generate annual pediatric antibiograms, a national composite antibiogram using existing institution-specific data can identify antibiotic susceptibility patterns relevant to children across the United States. Aggregating data from several antibiograms has been used successfully by state health departments in Alaska[11] and Washington state[20] and by the Veterans Affairs hospitals.[10]

The CLSI develops guidelines for antimicrobial susceptibility testing and antibiogram reporting.[13,19] In our study, the minority of institutions (16%) complied with the 6 CLSI recommendations that we evaluated, and compliance with

each individual measure varied between 16% and 91%. This is consistent with previous studies that have demonstrated substantial variability in approaches to constructing antibiograms.[21,22] The benefits of aggregated antibiograms underscore the importance of consistent methods of antibiogram preparation and reporting. For example, antibiograms that include duplicate bacterial isolates can overestimate resistance in those institutions, because patients with longer hospital stays and those who experience treatment failure tend to have cultures obtained more often than those who are infected with more susceptible organisms.[8,23-26] Improved compliance with CLSI guidelines would provide valuable data for both intrahospital and interhospital comparisons.

Noteworthy findings were observed regarding susceptibility patterns for some gram-negative organisms. Consistent with both national and international data based on organisms isolated from hospitalized adults, our results demonstrate poor activity of ampicillin-sulbactam against common enteric organisms such as *E. coli* and *K. pneumoniae*.[27,28] Interestingly, however, susceptibility to ampicillin-sulbactam has significantly improved in recent years in our cohort. As of 2009, the Surgical Infection Society and Infectious Diseases Society of America no longer advocate for ampicillin-sulbactam as an empirical treatment option for intra-abdominal infections.[29] Although we did not collect antibiotic usage data in our study, reduced selection pressure from decreased prescription of this agent may be a plausible explanation for these changes. Similarly, patterns of susceptibility to ciprofloxacin observed in our study may be reflective of patterns of use of these agents among children. In contrast with its use among adults, ciprofloxacin is used more conservatively in children, primarily as a consequence of osteoarticular adverse effects observed in juvenile animals.[30] The activity of ciprofloxacin against gram-negative pathogens in children appears to be higher than what has been reported for adults.[6,31-33] Because ciprofloxacin is prone to relatively rapid emergence of resistance with increased antibiotic pressure, it is important to continue to preserve its use, because it is one of the few oral agents available for treatment of *P. aeruginosa* infections.

Susceptibility patterns of other gram-negative agents appear to be similar to what has been described in the adult population. Ceftriaxone resistance is considered suggestive of chromosomally mediated AmpC β-lactamase resistance in
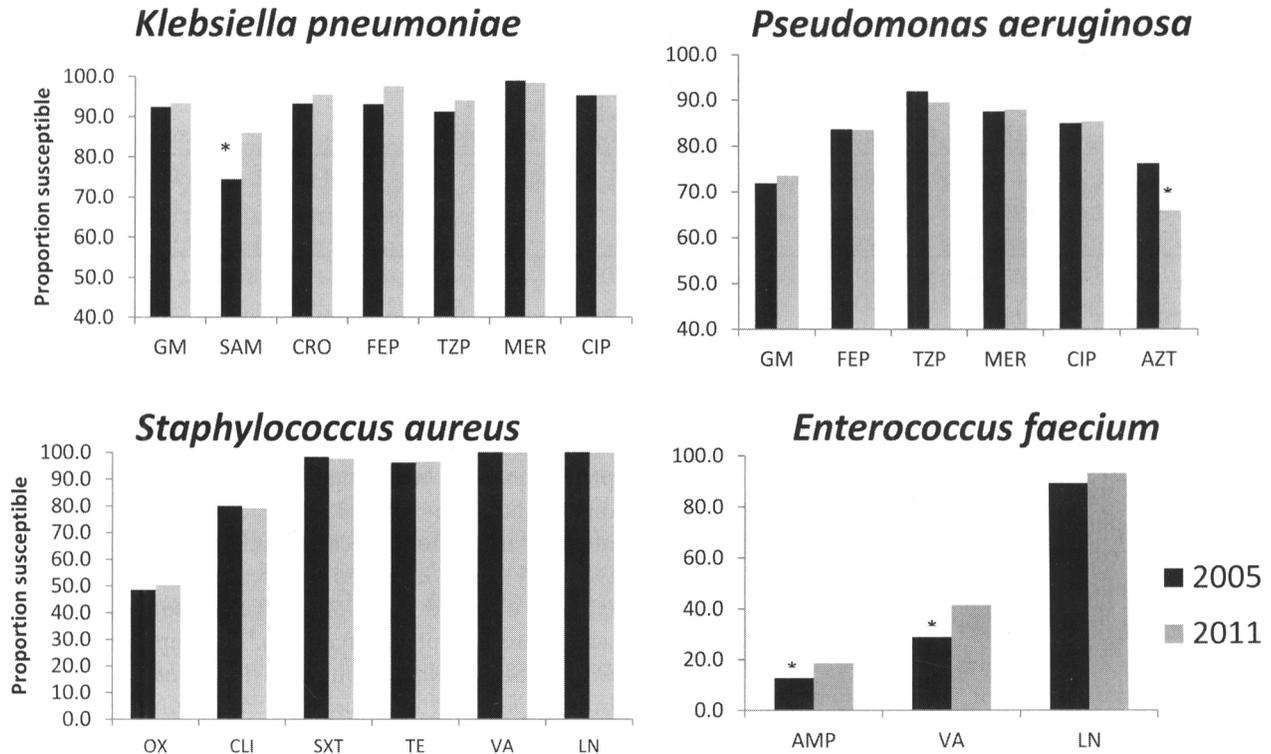
FIGURE 2.   Comparisons of antibiotic susceptibility proportions for specific microorganisms from 2005 through 2011 from pediatric antibiograms in the United States. AZT, aztreonam; CIP, ciprofloxacin; CLI, clindamycin; CRO, ceftriaxone; FEP, cefepime; GM, gentamicin; LN, linezolid; MER, meropenem/imipenem; OX, oxacillin; SAM, ampicillin-sulbactam; SXT, trimethoprim-sulfamethoxazole; TE, tetracycline; TZP, piperacillin-tazobactam; VA, vancomycin. $*P < .05$.

Enterobacter species.[15] Although the estimated prevalence of this mechanism among adult populations has been reported at 19%,[34,35] data regarding its prevalence among children are limited. Our study indicates that 22% of *Enterobacter* species were resistant to third-generation cephalosporins. Mirroring what has been observed in adults,[27,28,36] cefepime, piperacillin-tazobactam, and meropenem/imipenem appear to be reasonable treatment options for suspected infections due to most gram-negative organisms. Because none of the antibiograms submitted from 2011 incorporated the June 2011 breakpoint change for piperacillin-tazobactam against *Pseudomonas* species (≤ 64 μg/mL to ≤ 16 μg/mL), a decrease in the susceptibility of *Pseudomonas* species to piperacillin-tazobactam may emerge in antibiograms after 2011. Importantly, *P. aeruginosa* susceptibility to aztreonam was inferior to that of all β-lactams tested and has decreased significantly from 2005 to 2011. Caution should be used when aztreonam is prescribed empirically as monotherapy for children with serious infections potentially involving *P. aeruginosa*.

Susceptibility patterns for *S. aureus* have remained relatively stable from 2005 to 2011. Approximately one-half of all *S. aureus* isolates included in the 2010–2011 composite antibiogram were methicillin-resistant *S. aureus* (MRSA), but only 34% of such isolates in Western centers were MRSA. Overall susceptibility to clindamycin was 79%. However, we could not distinguish between community-acquired and hospital-acquired strains, and this may have resulted in overestimation and underestimation of hospital-acquired and community-acquired *S. aureus* susceptibility data, respectively. Fortunately, high susceptibility to trimethoprim-sulfamethoxazole, tetracycline, and vancomycin remained for both methicillin-susceptible *S. aureus* and MRSA. There were no isolates of vancomycin-intermediate or vancomycin-resistant *S. aureus* in our cohort.

Ampicillin susceptibility for *E. faecalis* was greater than 99%, suggesting that this drug remains a reliable first-line agent for treatment of presumed *E. faecalis* infection, in contrast to only 25% for *E. faecium*. Linezolid has been considered the drug of choice for vancomycin-resistant *E. faecium*, but it is concerning to see that, unlike data for adults, among whom resistance to linezolid has been reported to be very rare,[37-39] the prevalence of linezolid resistance approximated 8% among isolates obtained from children in our study. Because of the inability of antibiograms to capture cross-resistance of an isolate to multiple agents, we were unable to determine whether the *E. faecium* isolates that were resistant to linezolid retained susceptibility to vancomycin. Reasons for reduced linezolid susceptibility patterns in children are unknown but need to be investigated.

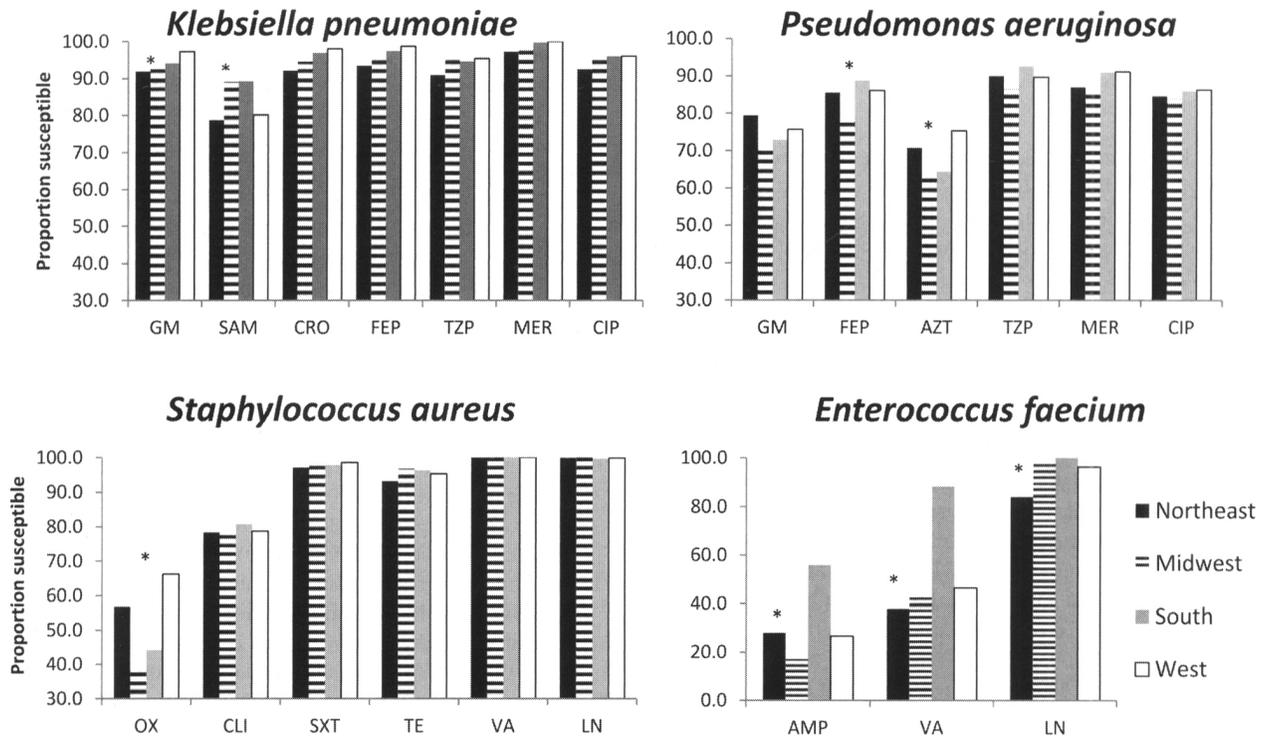There are some potential limitations to consider. First, we

FIGURE 3.   Regional comparisons of antibiotic susceptibility proportions for specific microorganisms from pediatric patients in the United States. AZT, aztreonam; CIP, ciprofloxacin; CLI, clindamycin; CRO, ceftriaxone; FEP, cefepime; GM, gentamicin; LN, linezolid; MER, meropenem/imipenem; OX, oxacillin; SAM, ampicillin-sulbactam; SXT, trimethoprim-sulfamethoxazole; TE, tetracycline; TZP, piperacillin-tazobactam; VA, vancomycin. $*P < .05$.

oversampled large academic centers and institutions located in the northeastern and western United States. However, until pediatric-specific antibiograms are more common among community hospitals and in all geographic regions, this will continue to be a challenge. Second, we could not assess differences in the underlying medical conditions of the children hospitalized in the various institutions, in antibiotic prescribing patterns between the contributing institutions, and differing antimicrobial susceptibility testing methods across microbiology laboratories. Finally, there are inherent limitations to antibiograms, such as their inability to account for emergence of resistance during therapy. In accord with the CLSI recommendations, most participating institutions include only first isolates in their antibiogram and do not account for the timing of the onset of infections. Thus, they may not be representative of resistance that evolves after prolonged exposure to the healthcare environment and likely underestimate resistance rates.[40] Because the utility of antibiograms may decrease as lengths of hospital stay increase, clinicians should seek additional guidance when selecting empirical antibiotic therapy for patients with prolonged hospitalizations.[40]

In summary, collating antibiograms appears to be a feasible and inexpensive method to understand antibiotic susceptibility prevalence estimates for children in the United States. Although antibiograms can be limited in their ability to capture resistance that develops upon antibiotic exposure or after

prolonged hospitalizations, they still can provide valuable data related to resistance trends and can inform future treatment guidelines. The ability to accurately represent pediatric drug susceptibility trends across the United States can be enhanced with involvement by all institutions caring for children. For laboratories not currently generating antibiograms, many automated health information systems and microbiology reporting systems are capable of summarizing these results with limited involvement of personnel. Moving forward, until funding is available for active surveillance, summarizing antibiograms over time can be a useful measure of susceptibility trends in children.

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