Pediatric-Specific Antimicrobial Susceptibility Data and Empiric Antibiotic Selection

**OBJECTIVE:** Duke University Health System (DUHS) generates annual antibiograms combining adult and pediatric data. We hypothesized significant susceptibility differences exist for pediatric isolates and that distributing these results would alter antibiotic choices.

**METHODS:** Susceptibility rates for *Escherichia coli* isolates from patients aged ≤12 years between July 2009 and September 2010 were compared with the 2009 DUHS antibiogram. Pediatric attending and resident physicians answered case-based vignettes about children aged 3 months and 12 years with urinary tract infections. Each vignette contained 3 identical scenarios with no antibiogram, the 2009 DUHS antibiogram, and a pediatric-specific antibiogram provided. Effective antibiotics exhibited >80% in vitro susceptibility. Frequency of antibiotic selection was analyzed by using descriptive statistics.

**RESULTS:** Three hundred seventy-five pediatric isolates were identified. Pediatric isolates were more resistant to ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) and less resistant to amoxicillin-clavulanate and ciprofloxacin (P < .0005 for all). Seventy-five resident and attending physicians completed surveys. In infant vignettes, physicians selected amoxicillin-clavulanate (P < .05) and nitrofurantoin (P < .01) more often and TMP-SMX (P < .01) less often with pediatric-specific data. Effective antibiotic choices increased from 68.8% to 82.2% (P = .06) to 92.5% (P < .01) across scenarios. In adolescent vignettes, providers reduced TMP-SMX use from 66.2% to 42.6% to 19.0% (P < .01 for both). Effective antibiotic choices increased from 32.4% to 57.4% to 79.4% (P < .01 and P = .01).

**CONCLUSIONS:** Pediatric *E. coli* isolates differ significantly in antimicrobial susceptibility at our institution, particularly to frequently administered oral antibiotics. Knowledge of pediatric-specific data altered empirical antibiotic choices in case vignettes. Care of pediatric patients could be improved with use of a pediatric-specific antibiogram. *Pediatrics* 2012;130:e615–e622
Appropriate antibiotic prescribing is essential to improve patient outcomes and to help prevent the emergence of resistant organisms. As has been noted for many years, resistance rates continue to rise with continued use of current antibiotics such that the eventual obsolescence of many of these agents is a major concern. Inappropriate antibiotics faster administration of appropriate have been shown for children with antibiotic susceptibility. In adults, following guidelines for pneumonia improves antibiotic selection and thus outcomes, and improved outcomes have been shown for children with faster administration of appropriate antibiotics. Inappropriate antibiotics are often broad spectrum, potentially leading to increased selection of resistant organisms. Susceptibility patterns may vary regionally and nationally as well as in different units within hospitals and between hospitals within health systems. Patterns of antibiotic resistance also vary within specific units and patient groups. Studies suggest that adults and children often have differences in resistance patterns for Escherichia coli, group A streptococci, Candida, and community-acquired methicillin-resistant Staphylococcus aureus. Access to the most accurate antimicrobial antibiogram for pediatric patients therefore would likely improve outcomes while limiting the risk of drug resistance.

At our institution, Duke University Medical Center, pediatric and adult patients are cared for in the same physical hospital structure (a “hospital-within-a-hospital”) with a single, shared microbiology laboratory. Annual antibiotic antibiograms are generated based on combined data from both adult and pediatric isolates. Given that these reports represent a collection of isolates that may not accurately represent those found in pediatric patients with commonly encountered infections, we hypothesized that there may be significant differences in resistance patterns when pediatric isolates were analyzed independently.

To test our hypothesis, we undertook a study of E. coli resistance patterns in the pediatric population at our institution to determine if resistance patterns differed significantly from those reported from hospital-wide isolates. To demonstrate further that these potential differences may affect the care of pediatric patients, we developed a case-based survey of pediatric providers within the health system to determine if the availability of pediatric-specific data would alter antibiotic selection.

METHODS
This protocol was reviewed and approved by the Duke Institutional Review Board (Pro00026893).

Comparison of Adult and Pediatric Susceptibility
Electronic medical record data were used to evaluate pediatric-specific culture data for all isolates of E. coli cultured in patients ≤12 years in the emergency department (ED), hospital, and outpatient settings between July 1, 2009, through September 30, 2010, within the Duke University Health System (DUHS). This was performed by using an automated electronic record review tool developed at our institution that allows for user-designed queries of electronic medical information. All inpatient, ED, and outpatient microbiology data are available via electronic medical record and are therefore accessible via electronic review. First, the cohort of patients aged ≤12 years who had a microbiological isolate of E. coli were identified. Data technicians at our institution were then able to extract antibiotic susceptibility results for these patients from the electronic medical record.

E. coli was chosen because it is the most frequently isolated pathogen from pediatric samples (predominantly urine). Twelve years of age was chosen as the age cutoff in an attempt to limit urine cultures from sexually active adolescents because these may be more similar to adult isolates in the community. For children with multiple positive cultures during the same hospitalization, only the first positive culture was used. Susceptibility percentages were then calculated for each antibiotic. The antibiotics for which susceptibility rates are reported are listed in Table 1. Third-generation cephalosporins (ceftriaxone) were reported only if the isolate was resistant to the first-generation alternative (cefazolin).

The Duke University Medical Center Clinical Microbiology Laboratory annually creates an antibiogram for multiple bacteria, including E. coli. The antibiotics for which susceptibilities were reported from 2009 are shown in Table 1. Comparison of rates of resistance between these 4314 samples and those obtained from database abstraction for children ≤12 years were derived by using a comparison of proportions assuming a binomial distribution.

Impact of Susceptibility Data on Provider Prescribing Practices
A survey assessing clinical treatment of acute urinary tract infections (UTIs) was distributed electronically to pediatric providers deemed most likely to treat acute UTIs: ED physicians, pediatric hospitalists, and other pediatric faculty that attend on the inpatient wards, primary care outpatient providers working in acute care clinics, and pediatric residents of all levels. Providers were asked to compare their training level and primary site of practice (inpatient vs outpatient vs ED).

This survey presented 2 clinical vignettes of children with probable UTIs, 1 in a 3-month-old child and 1 in a 12-year-old
child. Providers were asked to report antibiotic choices within each vignette. The survey text for these cases and additional information are shown in the Appendix.

The 2 cases (3-month-old and 12 year-old, both with UTIs) were presented 3 times on subsequent survey screens, each time asking identical questions regarding selection of antibiotics for each scenario. All cases were answered within the same survey administration. In Scenario A (first screen), no antibiotic resistance data were provided. In Scenario B (second screen), a chart of the hospital-wide 2009 Duke antibiogram for E. coli, Klebsiella, Pseudomonas, and Enterococcus were presented alongside the case. In Scenario C (final screen), a chart of the Duke pediatric-specific antibiogram obtained from our analysis of E. coli–positive cultures in children ≤12 years from 2009 was available. The screens were in the same order for all surveys administered, and participants could not return to previous screens after moving forward. Antibiotic selections were entered as free-text by providers. Effective antibiotics were considered to be those with >80% in vitro susceptibility rates because this is the cutoff for use of trimethoprim-sulfamethoxazole (TMP-SMX) as an empirical therapy in the most recent Infectious Disease Society of America guidelines for uncomplicated cystitis.

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**TABLE 1** Antibiotic Susceptibilities by Age Group

<table>
<thead>
<tr>
<th>Antibiotic (Pediatric n Tested)</th>
<th>Pediatric Isolates (% Susc)</th>
<th>Combined Isolates (% Susc, n = 4314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (306)</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Ampicillin (374)</td>
<td>45</td>
<td>57a</td>
</tr>
<tr>
<td>AMOX-CLAV/ampicillin-sulbactam (374)</td>
<td>83</td>
<td>59a</td>
</tr>
<tr>
<td>Ceftazolin (371)</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Ciprofloxacin (297)</td>
<td>91</td>
<td>81a</td>
</tr>
<tr>
<td>Gentamicin (374)</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>Imipenem (299)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Nitrofurantoin (338)</td>
<td>99</td>
<td>Not reported</td>
</tr>
<tr>
<td>Piperacillin-tazobactam (370)</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>Tobramycin (506)</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>TMP-SMX (374)</td>
<td>68</td>
<td>77a</td>
</tr>
</tbody>
</table>

*Susceptible.*

*P < .0005 for difference between pediatric and combined, all other *P* nonsignificant at >.05.

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Descriptive statistics were used to calculate frequency of response by antibiotic or antibiotic group (ie, first-generation cephalosporins) for each scenario by subset of antibiogram (scenario A vs B and A vs C) and by training level. Differences in survey response rates by antibiotic were assessed by using Fisher’s exact test, with cutoff for statistical significance at *P < .05*. All analyses were performed by using Stata v 9.2 (College Station, TX).

**RESULTS**

**Comparison of Adult and Pediatric Susceptibility**

Three hundred and seventy-five pediatric isolates were identified from 327 patients. Of these, most, but not all, were tested for each antibiotic. Demographic data for patients providing these isolates are shown in Table 2. Pediatric and hospital-wide antibiotic antibiograms are shown in Table 1. Pediatric isolates were more likely to be resistant to amoxicillin, amikacin, and TMP-SMX and less likely to be resistant to amoxicillin-clavulanate (AMOX-CLAV) and ciprofloxacin than the isolates generated from across age groups (*P < .0005 for all*).

Susceptibility to nitrofurantoin was not reported in the DUHS antibiogram though these data were available for the pediatric report.

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**Impact of Antibiograms on Provider Prescribing Practices**

To test for the potential utility of a pediatric-specific antimicrobial antibiogram on clinical practice, 92 categorical pediatrics and combined internal medicine-pediatrics residents were surveyed among 43 attending pediatricians. Surveys were completed by 49 residents (53%) and 26 attending physicians (61%), for an overall response rate of 56%.

**Three-Month-Old Female With UTI**

All but 1 provider initially chose to treat the 3-month-old female after urinalysis results were obtained. This provider reported that he or she would treat the patient on day 1 when culture results were positive. Of 74 pediatricians who chose to initiate antibiotics after the urinalysis was obtained, 3 reported they would change antibiotic therapy once they knew the organism was E. coli. Initial antibiotic choices for the 3 scenarios (no antibiogram, combined adult/pediatric data, and a pediatric-specific antibiogram) are presented in Table 3.

Comparing antibiotic choices between scenario A (no data) and scenario B (hospital-wide data), providers were more likely to choose a first-generation cephalosporin when presented with hospital-wide or pediatric-specific data. However, when pediatric-specific data were presented, providers were more likely to choose AMOX-CLAV and less likely to choose TMP-SMX.

Physicians were more likely to choose antibiotics only available in intravenous formulations when antibiotic antibiograms were provided compared with when no data were provided. In addition, 2 providers selected ciprofloxacin (not US Food and Drug Administration–approved for treatment of uncomplicated UTI in infants) when antibiograms were available, compared with no providers when data were not available.
When antiobiograms were not provided, only 68.6% of pediatricians selected an antibiotic with 80% or more in vitro efficacy against *E. coli* based on our pediatric data. This increased to 82.2% (P = .08 compared with no antiobiogram) when the combined antiobiogram was included in the scenario, and 92.5% when the pediatric-specific antiobiogram was available (P < .01 compared with no antiobiogram).

**Twelve-Year-Old Female With UTI**

Seventy-four providers responded to this set of cases. Four (5.4%) chose not to treat the 12-year-old female after the urinalysis result was obtained. Of 70 pediatricians who chose to initiate antibiotics after the urinalysis was obtained, only 3 reported they would change antibiotic therapy once they knew that the organism was *E. coli*.

Providers were significantly less likely to choose TMP-SMX when presented with the hospital-wide antiobiogram than when no data were available. Physicians were also significantly more likely to choose ciprofloxacin or nitrofurantoin than when no antiobiogram was available. Physicians were more likely to input antibiotics only available in intravenous or intramuscular formulations when hospital-wide and pediatric-specific antibiotic antiobiograms were available than when not presented with susceptibility information (13.2% and 9.5%, respectively, vs 0%; P < .01 for both). Antibiotic choices for the 3 scenarios (no antiobiogram, hospital-wide, and pediatric-specific antiobiograms) are presented in Table 4.

When antiobiograms were not included in the scenario, only 32.4% of pediatricians selected an antibiotic with 80% or more in vitro efficacy against *E. coli* based on our pediatric data. This increased to 57.3% when the combined antiobiogram was included in the scenario, a statistically significant increase (P < .01). When the pediatric antiobiogram was presented, the rate of provider selection of an effective antibiotic increased to 79.4%, a statistically significant improvement (P = .01).

**DISCUSSION**

In this study, we demonstrated significant differences in antimicrobial susceptibility in *E. coli* isolates obtained from pediatric patients relative to current hospital-wide published data at our institution. We subsequently demonstrated that presenting clinicians with this pediatric-specific information altered their clinical decision-making when choosing empirical therapy for children with UTI, with the more specific data increasing the theoretical efficacy of their empirical regimens. This 2-part study highlights several points about the need for and application of a pediatric-specific antiobiogram.

First, the finding of significant differences in antimicrobial susceptibility in pediatric isolates is not entirely new. It is known that susceptibility can vary by age, point of care (inpatient vs outpatient), and by inpatient ward. Our primary purpose in collecting this information at our institution was to gather data to support a change in our local practices for reporting these data. Currently, our clinical microbiology laboratory reports aggregated data for several thousand *E. coli* isolates from all sites in the hospital. Our hypothesis at the outset was that these data may not accurately represent the isolates causing infections in community-dwelling infants and adolescents. Accordingly, pediatric isolates at our institution have significantly lower rates of susceptibility to TMP-SMX and significantly higher rates of susceptibility to AMOX-CLAV than reported in aggregate data.

In our opinion, the rationale for not providing a pediatric-specific antiobiogram is weak. All the data required are already collected as part of database analysis.
tracking within our institution. Only an incremental extra effort to report the data for certain organisms or units is necessary. To better understand how our institution compares with peer institutions nationwide with regard to reporting antibiotic susceptibility patterns, we randomly contacted 10 pediatric “hospitals-within-hospitals.” These were selected by contacting every third institution sequentially from the list of 78 provided by the National Association of Children’s Hospitals and Research Institutions (10 responded). Overall, these institutions have a variety of practices: completely separating pediatric and adult data for internal dissemination (2 hospitals), separating only certain organisms (1 hospital), separating data only for the intensive care nursery (1 hospital), or reporting data together regardless of age or ward (6 hospitals). Proponents of pediatric quality of care initiatives and also of antimicrobial resistance control should advocate for the simple step of universal pediatric reporting in their efforts toward improvement. Lack of pediatric representation in clinical microbiology leadership, lack of specific data documenting the utility of offering pediatric specific antimicrobial susceptibility, potential cost increases, and lack of advocacy on the part of pediatric practitioners demanding these data are likely reasons for such reports not being offered more widely.

When examining the results of provider choices of empirical antibiotic therapy in the UTI vignettes in our survey, a few key points are highlighted. First, antibiotic choices differed less with the addition of DUHS antibiogram data to the scenario than with a change from DUHS antibiogram data to our pediatric data. We think this is largely because our practitioners had been conditioned with hospital-wide data and therefore were already incorporating these results into their practices and management. When practitioners were then provided with pediatric-specific data, their choices reflected the more specific data.

Additionally, with the increased rates of resistance to TMP-SMX and AMOX, practitioners shifted their choices to alternative agents. For the infant case vignette, smaller trends in antibiotic changes were evidenced because most providers initially chose a first- or third-generation cephalosporin, to which the isolates were largely susceptible. For the 12-year-old patient vignette, the changes were more magnified as pediatric-specific data shifted the choices from TMP-SMX to other agents with increased susceptibility. Although some individual antibiotic switch rates, even if statistically significant, may not be clinically meaningful, the overall trend to reduce TMP-SMX use is both statistically significant and clinically meaningful. In our study population, TMP-SMX was a common choice of initial empirical antibiotic in the infant vignette (26%) and the most commonly chosen initial empirical antibiotic (66%) in our adolescent vignette. Although TMP-SMX remains the most prescribed antibiotic for pediatric UTIs nationally,17 its use declined by 78% in infants and 73% in adolescents as increasingly specific antibiograms were provided. This shift in prescriptions led to a theoretical improvement in potential outcomes because the number of prescriptions for antibiotics with >80% in vitro–susceptible isolates increased significantly in both vignettes.

Our results also highlight a potential downside to antibiograms, which is that more data may not always lead to better choices. Several respondents selected highly potent IV antibiotics for these case vignettes (eg, amikacin) when other more appropriate agents were available. Others selected nitrofurantoin for the treatment of young infants when this drug is not recommended because of poor serum concentrations to treat potentially associated bacteremia. We attribute these findings to the relative inexperience of the practitioners taking the survey, several of whom were pediatric interns. However, although no attending physicians chose aminoglycosides or nitrofurantoin, similar proportions of attending physicians and residents chose intravenous or intramuscular antibiotics for the 3-month-old patient, and 1 attending chose ciprofloxacin. These issues can be counteracted by adjusting reporting to reflect inpatient versus outpatient collection of the isolate, age of the

### TABLE 4 Antibiotic Selection for a 12-Year-Old Female With UTI, by Scenario

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Scenario A: No Data (n = 68)</th>
<th>Scenario B: Hospital-wide Data (n = 68)</th>
<th>Scenario C: Pediatric-Specific Data (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside, (%)</td>
<td>0</td>
<td>3 (4.4)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Amoxicillin, (%)</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>AMOX-CLAV, (%)</td>
<td>0</td>
<td>0</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Ciprofloxacin, (%)</td>
<td>1 (1.5)</td>
<td>6 (8.8)</td>
<td>8 (12.7)*</td>
</tr>
<tr>
<td>Nitrofurantoin, (%)</td>
<td>1 (1.5)</td>
<td>0</td>
<td>12 (19.0)*</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam, (%)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>TMP-SMX, (%)</td>
<td>45 (66.2)</td>
<td>29 (42.6)a</td>
<td>12 (19.0)b</td>
</tr>
<tr>
<td>First-generation cephalosporin, (%)</td>
<td>10 (14.7)</td>
<td>19 (27.9)</td>
<td>15 (23.8)</td>
</tr>
<tr>
<td>Third-generation cephalosporin, (%)</td>
<td>10 (14.7)</td>
<td>9 (13.2)</td>
<td>9 (14.3)</td>
</tr>
<tr>
<td>Cephalosporin, NOS, (%)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Antibiotic with &gt;80% effectiveness, (%)</td>
<td>22 (32.4)</td>
<td>39 (57.3)d</td>
<td>50 (79.4)c</td>
</tr>
<tr>
<td>Intravenous only</td>
<td>0</td>
<td>9 (13.2)d</td>
<td>6 (9.5)c</td>
</tr>
</tbody>
</table>

NOS, not otherwise specified.

a P < .05.

b P < .01 for comparison between scenario A (no data) and scenario C (pediatric-specific data).

c P < .01 for comparison between scenario A (no data) and scenario B (adult/pediatric combined data).
patient, or purposefully reporting only oral options if they are susceptible (hierarchical reporting), for example. Reporting of antimicrobial susceptibility for several organisms (e.g., *Streptococcus pneumoniae* intermediate susceptibility in blood versus cerebrospinal fluid) already takes these issues into account, so these adjustments could also be made in pediatric cases. Additionally, with the increasing use of electronic ordering protocols, choices can be offered that direct providers to preferred agents for particular age groups and oral alternatives, as well as reminding providers of the most frequent causative agents. In the case of first-generation cephalosporins, for which susceptibility to a popular intravenous formulation, cefazolin, may not translate into similar susceptibility of oral formulations, additional susceptibility testing in the microbiology laboratory could be undertaken.

Our results must be examined in light of certain limitations. We performed an analysis of 1 year’s worth of data for 1 organism in pediatric patients at our institution, which may have skewed our results. Broader studies of pediatric specific antimicrobial susceptibility should be conducted examining multiple organisms over multiple years. Additionally, we performed a survey of practitioners at our own institution. This is a small number of physicians, and although our response rate was good, our sample size is small. Also, this survey evaluated preferences as stated in a survey, not actual prescribing patterns, which may differ. Finally, 2 scenarios within each vignette involved presentation of antibiograms with specific antibiotics listed, which may have led to different choices (such as nitrofurantoin in infants or more frequent intravenous therapies) given this visual prompt. It is possible that we may have biased the selections made by practitioners based on the presentation of the data. Finally, *E. coli* was chosen as the most frequently isolated pediatric pathogen. Less frequently encountered organisms would generate less precise estimates given smaller denominators and may need to be combined with adult data to achieve sufficient numbers to report. Also, care must be taken in using antibiograms because in vitro sensitivity data do not account for drug concentration in the urine and therefore do not always accurately predict in vivo response.

**CONCLUSIONS**

We demonstrated significant differences in pediatric isolates of *E. coli* at our institution with regard to antimicrobial susceptibility. By using these data, we found that knowledge of pediatric-specific data altered the prescribing choices of empirical antibiotic treatment in 2 UTI patient case vignettes. Our results suggest that care of pediatric patients could be improved by more widespread use of pediatric specific antibiograms. Given the lack of additional resources required of clinical microbiology laboratories, pediatric providers should urge their own laboratories to make this data available.

**ACKNOWLEDGMENTS**

We thank the pediatric house staff and faculty at Duke University Medical Center for their participation in this project. We also thank Tara McKellar for assistance in preparing clinical research documents and Pat Seed and Michael Cohen-Wolkowiez for critical review of the manuscript.

**REFERENCES**


APPENDIX Survey Questions for Each Case

1. You are seeing a 3-month-old female infant in same day clinic with fever (101.0°F). She is well-appearing. Urinalysis obtained from straight cath shows:
   1+ Leukocyte esterase
   2+ Nitrites
   12 White Blood Cells
   >50 bacteria
   Your laboratory will automatically culture the results and provide susceptibilities in 2 days. Would you give this child antibiotics?
   Yes
   No
   If yes, WHICH ANTIBIOTIC (please list only 1)?

2. Urine grows out >100,000 colonies of E. coli on day 1. Does this change your initial management?
   Yes
   No
   If yes, HOW?

3. Your next patient is a 12 y-old female with dysuria. She is well-appearing. Urinalysis obtained from clean catch shows:
   1+ Leukocyte esterase
   2+ Nitrites
   12 White blood cells
   >50 bacteria
   Your laboratory will automatically culture the results and provide susceptibilities in 2 days. Do you give this child antibiotics?
   Yes
   No
   If yes, WHICH ANTIBIOTIC (please list only 1)?

4. Urine grows out >100,000 colonies of E. coli on day 1. Does this change your initial management?
   Yes
   No
   If yes, HOW?
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