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Jeffrey S. Gerber, Jason G. Newland, Susan E. Coffin, Matt Hall, Cary Thurm, Priya A. Prasad, Chris Feudtner and Theoklis E. Zaoutis

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AUTHORS: Jeffrey S. Gerber, MD, PhD,[a,b] Jason G. Newland, MD,[c] Susan E. Coffin, MD, MPH,[a,b,d] Matt Hall, PhD,[e] Cary Thurm, PhD,[e] Priya A. Prasad, MPH,[a] Chris Feudtner, MD, PhD, MPH,[b,d,f] and Theoklis E. Zaoutis, MD, MSCE[a,b,d]

Divisions of [a]Infectious Diseases [f]General Pediatrics, and the [b]Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [d]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [c]Division of Infectious Diseases, Children's Mercy Hospital, Kansas City, Missouri; and [e]Child Health Corporation of America, Shawnee Mission, Kansas

KEY WORDS

antimicrobials, children, hospital, variability

ABBREVIATIONS

PHIS—Pediatric Health Information System

CMI—case-mix index

ICD-9—*International Classification of Diseases, Ninth Revision*

DOT—days of therapy

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Address correspondence to Jeffrey S. Gerber, MD, PhD, Division of Infectious Diseases, Children's Hospital of Philadelphia, CHOP North, Suite 1518, Philadelphia, PA 19104. E-mail: gerberj@email.chop.edu

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WHAT'S KNOWN ON THIS SUBJECT: National organizations recommend the implementation of antimicrobial stewardship programs (ASPs) to help facilitate the judicious use of antibiotics within hospitals. Establishing guidelines for an ASP relies on the comparison of use across equivalent institutions to identify high-impact targets for improvement.

WHAT THIS STUDY ADDS: Both the quantity and type of antibiotic-prescribing ranged broadly across US children's hospitals. These data will help establish benchmarks for the judicious use of antibiotics within children's hospitals and help target research to identify reasons for such variability.

abstract

BACKGROUND: Variation in medical practice has identified opportunities for quality improvement in patient care. The degree of variation in the use of antibiotics in children's hospitals is unknown.

METHODS: We conducted a retrospective cohort study of 556 692 consecutive pediatric inpatient discharges from 40 freestanding children's hospitals between January 1, 2008, and December 31, 2008. We used the Pediatric Health Information System to acquire data on antibiotic use and clinical diagnoses.

RESULTS: Overall, 60% of the children received at least 1 antibiotic agent during their hospitalization, including >90% of patients who had surgery, underwent central venous catheter placement, had prolonged ventilation, or remained in the hospital for >14 days. Even after adjustment for both hospital- and patient-level demographic and clinical characteristics, antibiotic use varied substantially across hospitals, including both the proportion of children exposed to antibiotics (38%–72%) and the number of days children received antibiotics (368–601 antibiotic-days per 1000 patient-days). In general, hospitals that used more antibiotics also used a higher proportion of broad-spectrum antibiotics.

CONCLUSIONS: Children's hospitals vary substantially in their use of antibiotics to a degree unexplained by patient- or hospital-level factors typically associated with the need for antibiotic therapy, which reveals an opportunity to improve the use of these drugs. *Pediatrics* 2010;126:1067–1073

The inappropriately excessive use of antimicrobial agents, particularly systemic antibiotic agents, is a major public health and patient safety issue. Most hospitalized patients receive antibiotics,[1–4] and roughly one-half of all antibiotic use is unnecessary.[5] Antibiotic overuse promotes the emergence and expansion of antibiotic-resistant organisms,[5,6] and infections caused by resistant pathogens have a significant impact on patient morbidity and mortality,[7–9] with an estimated cost of $4 billion to $5 billion annually.[10] In addition, the range and frequency of adverse drug effects caused by antibiotic use have been well documented.[11–17]

Professional guidelines strongly recommend the judicious use of antibiotics to prevent the emergence and transmission of multidrug-resistant organisms.[6] In addition, the Infectious Diseases Society of America has urged action to combat the epidemic of antibiotic-resistant infections and has published guidelines for developing institutional programs to enhance antimicrobial stewardship.[5,18] Supported by many professional organizations, including the Pediatric Infectious Diseases Society, the primary goal of these guidelines is to optimize clinical outcomes and reduce the drug toxicity and antimicrobial resistance associated with the excessive use of these agents.[5]

Establishing specific prescribing benchmarks to guide antimicrobial stewardship programs for hospitalized children relies on the comparison of use across equivalent institutions to identify high-impact targets for improvement. To begin this process, we constructed a large, geographically diverse cohort to describe the variability in antibiotic use in US children's hospitals. The results of our analyses will help identify high-impact targets for focused efforts to optimize use of these agents in children.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study of pediatric inpatients using the Pediatric Health Information System (PHIS), an administrative database managed by the Child Health Corporation of America that contains inpatient data from >40 freestanding US children's hospitals. We included all patients discharged from the 40 PHIS hospitals that contributed pharmacy data between January 1, 2008, and December 31, 2008. The PHIS database contains detailed information for each patient hospitalization, including demographics, diagnoses, medications, procedures, and laboratory tests. Member hospitals represent 17 of the 20 major metropolitan areas across the United States, with only 1 children's hospital representing each city. On the basis of estimates from the National Association of Children's Hospitals and Related Institutions (Alexandria, VA), 70% of freestanding pediatric acute care hospital admissions in the United States is reported in the PHIS database.

Data quality and reliability are assured through a joint effort between Child Health Corporation of America, a data manager (Thomson-Reuters, Durham, NC), and participating hospitals. PHIS data are deidentified at the time of submission (before data extraction and analysis) and are accepted into the database only when classified errors occur in fewer than 2% of a hospital's quarterly data. During the study, 100% of drug use data from all hospitals that submit resource use data was included.

Independent Variables

Institution-level variables included geographic location, average daily census, and number of staffed beds. Patient-level variables identified for each hospital admission included age (0–29 days, 30–364 days, 1–4 years, 5–11 years, and 12–17 years), gender, race (non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other), and discharge disposition. Resource use data included length of hospital stay and case-mix index (CMI), a widely used surrogate for severity of illness and risk of mortality. CMI in PHIS is based on all patient-refined diagnosis-related group categories and severity levels and is calculated by Thomson-Reuters as the ratio of the average charge for patients in a particular all patient-refined diagnosis-related group category/severity level combination to the average charge for all patients who use their national pediatric database. Mechanical ventilation status (yes/no), ventilation days (0, 1–3, 4–18, >18), and ICU stay (yes/no) were based on charge data.

International Classification of Diseases, Ninth Revision (ICD-9) diagnosis or procedure codes were used to identify the occurrence of infection (defined by the presence or absence of any code(s) for microbial, fungal, viral, or parasitic infections), surgery (yes/no), and central-line catheter placement (yes/no). The presence of concurrent chronic illnesses was assessed by using an established and validated method for characterizing ICD-9-based pediatric complex chronic conditions, represented by 9 categories: neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic or immunologic, metabolic, malignancy, and genetic or other congenital defect conditions, described by Feudtner et al.[19]

Dependent Variables

For this study, we defined antibiotic use by the presence of hospital billing data for any systemic antibacterial drug. We considered vancomycin, cefepime, piperacillin/tazobactam, ticarcillin/clavulanate, carbapenems (imipenem, meropenem, ertapenem), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin), and linezolid to be "broad-spectrum" agents. Although classifying antibiotics by breadth of activity is inherently subjective and, consequently, reasonably debated, our intent was to identify drugs most commonly used to empirically treat critically ill patients, or those used for the targeted or empiric therapy of antibiotic-resistant infections. Dependent variables included receipt of any systemic antibiotic agent or broad-spectrum antibiotic agent (yes/no) and the number of days the patient received any antibiotic agent or broad-spectrum antibiotic agent.

Statistical Analysis

Categorical variables were summarized using frequencies and percents for all patients included in the study, including (1) the proportion of patients in each group who received any antibiotics and (2) the proportion of antibiotic orders that were broad-spectrum (as defined above). Adjusted hospital-specific use rates (the percentage of patients who received antibiotic agents or per 1000 patient-days) were calculated using generalized linear mixed effects models, controlling for hospital clustering and allowing for the presence of correlated data (within hospitals), nonconstant variability (across hospitals), and responses that are not normally distributed. Quasi-likelihood estimation for proportions with unknown distributions was used to model the duration of antibiotic use, defined as the proportion of total days of an admission that a patient received antibiotic therapy, for all patients and for only those patients who received antibiotic agents. Proportional use and 95% confidence intervals are reported by hospital. Discharge level resource use was controlled for by use of length of stay as an independent variable.

SAS 9.1 (SAS Institute, Inc, Cary, NC) was used for all analyses, and $P < .001$ was considered statistically significant because of the large sample sizes used to conduct the analysis.

TABLE 1 Hospital Characteristics

	No. (%) of Hospitals ($N = 40$)
Census region	
Northeast	5 (12.5)
South	15 (37.5)
North central	11 (27.5)
West	9 (22.5)
Average daily census	
<150	10 (25.0)
150–200	17 (42.5)
>200	13 (32.5)
No. of beds	
<200	9 (22.5)
200–300	22 (55.0)
>300	9 (22.5)

RESULTS

A total of 556 692 discharges from 40 children's hospitals from January 1, 2008, through December 31, 2008, were analyzed. Hospital characteristics including census region, average daily census, and number of beds are summarized in Table 1. The demographic and clinical characteristics of these children and the hospitals from which they were discharged, as well as the proportion of children with each of these characteristics who were given antibiotics, are displayed in Table 2.

Unadjusted analyses revealed that 60% of hospitalized children received at least 1 dose of an antibiotic, and, on average, antibiotics were given for 468 per 1000 patient-days. Antibiotics were ordered for at least 90% of patients who had surgery, underwent central venous catheter placement, had prolonged ventilation, or remained in the hospital for >14 days. Of children who received antibiotics, broad-spectrum agents were chosen more often in those who stayed in the ICU, received prolonged ventilation, underwent central venous catheter placement, had a longer length of stay, or received care in an institution with a higher CMI (Table 2).

To compare use across hospitals, we adjusted for the patient-level and hospital-level characteristics listed in Table 2. After adjusting for these factors, significant variability in antibiotic use remained. To illustrate this, we used 2 different measures of adjusted antibiotic use. First, considering the proportion of children who were prescribed an antibiotic at any point during their hospitalization, the adjusted institutional rate of antibiotic use was calculated (overall use). As illustrated in Fig 1A (x-axis), adjusted use ranged from 38% to 72% of admissions. By this measure, children admitted to the highest-using quartile of hospitals were, on average, 27% more likely to receive an antibiotic than those admitted to the bottom quartile of hospitals, and children admitted to the highest-using 10% of hospitals were, on average, 44% more likely to receive an antibiotic than those admitted to the lowest-using 10% of hospitals.

Second, accounting for the same patient-level and hospital-level variables, we calculated the adjusted days of antibiotic exposure in children (Fig 1A, y-axis). Using this metric, adjusted use ranged from 368 to 601 per 1000 patient-days. By this measure, children admitted to the highest-using quartile of hospitals were 25% more likely to receive an antibiotic than those admitted to the bottom quartile of hospitals, and children admitted to the highest-using 10% of hospitals were 37% more likely to receive an antibiotic than those admitted to the lowest-using 10% of hospitals. Examining the relationship between overall use and days of therapy revealed a positive correlation between these 2 metrics; thus, in general, hospitals that exposed more individual patients to antibiotics also exposed their patients to more days of therapy (Fig 1A; $P < .001$).

To further explore the differences in antibiotic use across institutions, we re-

TABLE 2 Unadjusted Antibiotic Use Across Children's Hospitals According to Demographic and Clinical Variables Used for Adjustment in the Multivariable Model

Descriptor	Overall, *n* (%)	Received Any Antibiotic, *n* (%)	Received Broad-Spectrum Antibiotics, *n* (%)
Total	556 692 (100)	336 088 (60.4)	70 037 (20.8)
Infection diagnosis	208 268 (37.4)	162 256 (77.9)	46 730 (28.8)
ICU stay	104 728 (18.8)	81 599 (77.9)	27 825 (34.1)
Female	249 979 (44.9)	152 207 (60.9)	31 202 (20.5)
Surgical status	143 294 (25.7)	128 644 (89.8)	27 015 (21)
Central-line catheter	41 844 (7.5)	39 431 (94.2)	20 386 (51.7)
Non-Hispanic white	265 595 (49)	159 038 (59.9)	35 147 (22.1)
Non-Hispanic black	115 027 (21.2)	65 707 (57.1)	12 222 (18.6)
Hispanic	104 113 (19.2)	66 719 (64.1)	13 611 (20.4)
Asian	13 405 (2.5)	8053 (60.1)	1667 (20.7)
Other	43 679 (8.1)	26 944 (61.7)	5470 (20.3)
Ventilation			
0 d	533 351 (95.8)	315 099 (59.1)	60 499 (19.2)
1–3 d	13 059 (2.3)	11 137 (85.3)	3876 (34.8)
4–18 d	8075 (1.5)	7668 (95.0)	3949 (51.5)
>19 d	2207 (0.4)	2184 (99.0)	1795 (82.2)
Disposition			
Home	527 623 (95)	31 4217 (59.6)	60 015 (19.1)
Died	4513 (0.8)	3997 (88.6)	2666 (66.7)
Other	23 168 (4.2)	17 266 (74.5)	7131 (41.3)
Complex chronic conditions diagnoses			
Neurologic	49 046 (8.8)	32 143 (65.5)	10 543 (32.8)
Cardiovascular	49 531 (8.9)	36 525 (73.7)	12 711 (34.8)
Respiratory	15 702 (2.8)	11 526 (73.4)	4495 (39)
Renal	9274 (1.7)	8013 (86.4)	1827 (22.8)
Gastrointestinal	11 473 (2.1)	8616 (75.1)	2947 (34.2)
Metabolic	9364 (1.7)	6333 (67.6)	2831 (44.7)
Hematologic/immunologic	8613 (1.5)	5513 (64.0)	2145 (38.9)
Malignancy	44 849 (8.1)	33 062 (73.7)	12 365 (37.4)
Congenital/genetic	25 355 (4.6)	19 412 (76.6)	5416 (27.9)
Length of stay			
1–2 d	194 643 (35)	86 435 (44.4)	7174 (8.3)
3–7 d	269 811 (48.5)	171 273 (63.5)	27 575 (16.1)
8–14 d	51 252 (9.2)	41 030 (80.1)	13 950 (34)
>14 d	40 986 (7.4)	37 350 (91.1)	21 140 (56.6)
Age group			
0–29 d	120 044 (21.6)	68 167 (56.8)	16 019 (23.5)
30 d–364 d	62 008 (11.1)	39 541 (63.8)	7987 (20.2)
1–4 y	98 726 (17.7)	59 695 (60.5)	11 641 (19.5)
5–11 y	145 259 (26.1)	89 572 (61.7)	18 273 (20.4)
12–17 y	130 655 (23.5)	79 113 (60.6)	15 506 (19.6)
Census region			
Northeast	69 230 (12.4)	43 442 (62.8)	10 122 (23.3)
South	218 457 (39.2)	132 246 (60.5)	26 846 (20.3)
North central	157 805 (28.3)	92 380 (58.5)	18 199 (19.7)
West	111 200 (20)	68 020 (61.2)	14 828 (21.8)
CMI			
Low	99 525 (17.9)	30 384 (30.5)	1914 (6.3)
Moderately low	165 430 (29.7)	88 580 (53.5)	10 984 (12.4)
Moderately high	149 834 (26.9)	94 295 (62.9)	14 710 (15.6)
High	141 903 (25.5)	122 829 (86.6)	42 130 (34.3)

peated these adjusted analyses considering exposure to broad-spectrum antibiotic agents (as a subset of children exposed to antibiotics). As illustrated in Fig 1B, variation in the use of broad-spectrum antibiotics mirrored that seen with overall antibiotic use, as measured by both overall use and days of therapy. As was the case when considering all antibiotic classes, the relationship between overall use and days of therapy with broad-spectrum antibiotics again revealed a positive correlation between these 2 metrics (Fig 1B; $P < .001$). In addition, there was a positive correlation between the proportion of children prescribed any antibiotics and the proportion given broad-spectrum agents ($P = .017$), which indicates that, in general, institutions that prescribe more antibiotics also used more broad-spectrum antibiotics (inconsistent with the notion that more overall antibiotic exposure was compensated for by the preferred use of narrow-spectrum therapy). Although all patient and clinical variables listed in Table 2 were adjusted for in these analyses, the standardized β coefficients derived from these adjustments revealed that performance of a surgical procedure (0.32), presence of an infection code (0.32), and hospital CMI (0.18) were most influential; all other standardized β values were $\leq$0.7.

DISCUSSION

To our knowledge, this study is the first to compare antibiotic use across children's hospitals. We found that 60% of hospitalized children are prescribed at least 1 antibiotic, and that antibiotics were given for an average of 468 of 1000 inpatient-days. When examined by hospital, however, significant variability in antibiotic use becomes apparent: after extensive adjustment for both patient and hospital level characteristics, children at some institutions were 44% more likely to receive antibiotics or, using an alternative metric, were exposed to antibiotics for 37% more days when compared with other institutions.

Although outpatient antibiotic-prescribing has been relatively well characterized,[20–25] the data that describes inpatient antibiotic use are limited. Antibiotic use has been measured among networks

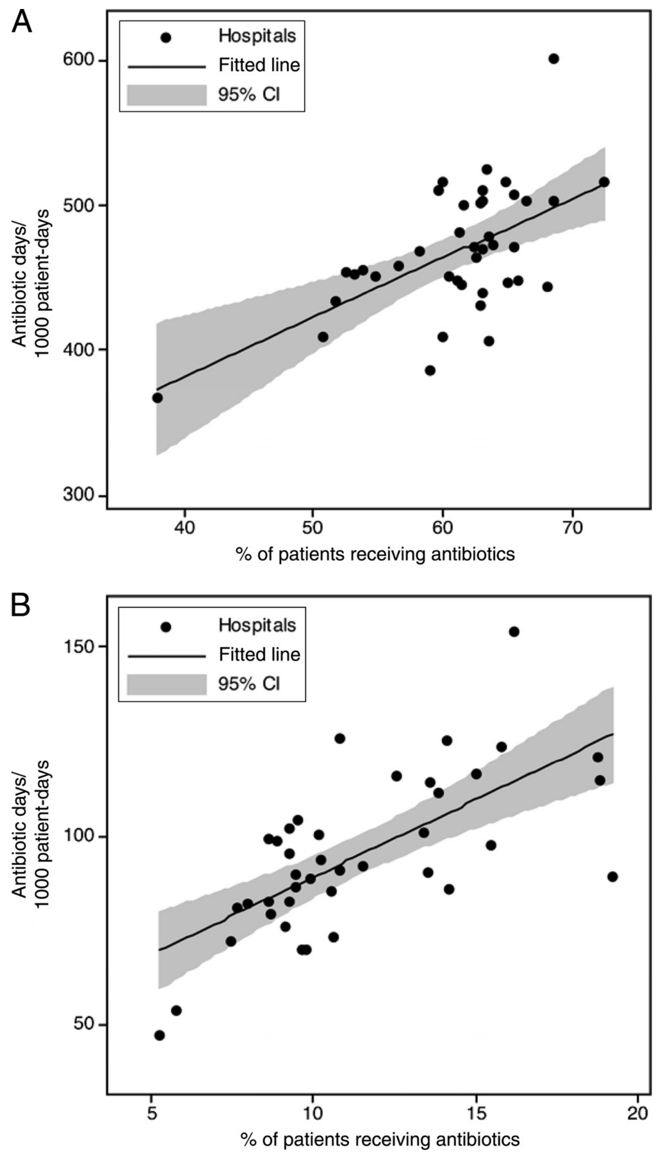

FIGURE 1

Adjusted antibiotic use per 1000 patient-days versus any use during a hospitalization. A, All antibiotics; B, broad-spectrum antibiotics.

of hospitals, including Centers for Disease Control and Prevention initiatives such as the National Nosocomial Infection Surveillance System[26] and Project Intensive Care Antimicrobial Resistance Epidemiology;[27] however, these programs analyzed exclusively ICU admissions and a relatively small proportion of children. In addition, antibiotic use in these reports is quantified as "defined daily doses" per 1000 patient-days, a metric unsuitable for children because children's medications are dosed on the basis of weight. More recently, the number of days of therapy (DOT) has been proposed as an alternative measure of antimicrobial use that may allow more appropriate comparisons of antimicrobial use between adults and children.[1] Adopting this approach, investigators found that 60% of hospitalized adults received at least 1 dose of antibiotic therapy and that inpatients received an average of 776 per 1000 patient-days of therapy. Comparing use across these hospitals in a subsequent analysis, the same group reported that the proportion of inpatients who received at least 1 dose of an antibiotic agent during their hospitalization demonstrated a range across hospitals of 44.4% to 73.6%, whereas the mean total rate of antibiotic use ranged between 454 and 1153 per 1000 patient-days (multiple antibiotics on the same day each count individually as 1 DOT, which allows the total DOT numerator to exceed 1000).[2] Again, however, these studies analyzed adult patients without subset analyses of children.

Only 2 studies have focused exclusively on antibiotic use in hospitalized children. A point prevalence survey, which included only ICU patients, identified that ~71% of NICU patients and 43% of PICU patients were receiving antibiotics at the time of the survey.[28] The authors of the lone pediatric-specific study of all hospitalized children (not confined to the ICU) described discharges from 20 academic hospitals throughout the United States.[29] This study identified a mean of 33% of children as exposed to at least 1 antibiotic during their hospitalization and ~550 DOT per 1000 patient-days. These academic hospitals, however, served primarily adult patients and, after excluding adults from the analysis, there were 30-fold fewer children per year than were included in our study of 40 freestanding children's hospitals. In addition, the analysis did not compare antibiotic use between institutions.

The striking variability in antibiotic use revealed by our analysis persisted despite adjustment for patient characteristics associated with an increased need for antibiotic therapy or prophylaxis (infection diagnosis, surgical procedures, ICU stay, ventilator days, and underlying chronic conditions) as well as for hospital characteristics (summarized by the CMI), suggestive of an institution that may provide more advanced care to a generally sicker population and, therefore, require more empiric or targeted antibiotic therapy. In addition, our analysis included children who were admitted to exclusively freestanding children's hospitals throughout an entire year, representing a relatively homogeneous group of centers with respect to the need and expertise available for the treatment of infectious diseases. In addition, hospitals that exposed a higher proportion of patients to antibiotics also used more days of therapy, a relationship inconsistent with the notion that institutions at which more patients are exposed to antibiotics use these drugs for shorter periods of time, or vice versa. Also, hospitals that used more antibiotics, measured either by overall use or days of therapy, tended to (aggregately) use more vancomycin, cefepime, piperacillin/tazobactam, ticarcillin/clavulanate, carbapenems, fluoroquinolones, and linezolid as a proportion of total antibiotic use than did lower-using centers, negating the possibility that antibiotic quantity was generally offset by limiting patient exposure to these broad-spectrum drugs (and the associated increased antibiotic resistance pressure and cost).

Although it is unclear what factors specifically drove increased antibiotic use within higher-using hospitals, variability was apparent in both the percentage of children who received an antibiotic agent at any time during their hospitalization as well as in total days of antibiotics received. Thus, either a lower threshold to institute treatment with antibiotics or a longer length of therapy for a given condition (or both) could have contributed. Notably, many children who received antibiotic agents did not have a diagnosis code for infection. Although some of these patients may have received appropriate surgical prophylaxis, variability in the threshold to begin (or continue) antibiotics for conditions ultimately not diagnosed as infectious could account for this phenomenon.

Although not surprising, such profound variability in antibiotic use is troubling. If variability remains after normalizing for differences in illness severity and patient complexity, it follows that either children at some hospitals are undertreated with antibiotics and, therefore, are unnecessarily at risk of treatment failure or, the more likely alternative, that some hospitalized children receive excessive antibiotic therapy and therefore are unnecessarily at risk of developing antibiotic-resistant infections and drug-related adverse effects while incurring inappropriate hospital costs. In addition to highlighting the need to establish effective antibiotic stewardship programs in children's hospitals, a setting in which there remains considerable opportunity for improvement,[30] these data provide further impetus to perform comparative effectiveness studies to determine the appropriate therapy, particularly with respect to duration of antibiotic therapy, for common pediatric infections.[31] More detailed analyses of these data to identify specific agents and indications associated with the greatest variability will provide high-impact targets for improvement.

Our study has limitations. The PHIS database offers the unique advantage of detailed, national-level, pediatric data from the majority of US metropolitan areas. PHIS provides up to 21 diagnosis codes per hospitalization, which provides more diagnosis data per patient than most administrative data sets. This database, however, may not be generalizable to nontertiary care, freestanding children's hospitals. For example, because of referral bias, PHIS may overrepresent the true incidence of some medically complicated or severe infections. Also, administrative data sources such as PHIS are limited with specific regard to the possibility of miscoded or inaccurate information. Although generally specific, identification based on ICD-9 Clinical Modification may not have ideal sensitivity. In this study, however, we did not rely heavily on ICD-9-based coding, including the dependent and the majority of independent variables, and the use of ICD-9 codes to identify chronic complex conditions has been validated.[19] In addition, all data benefited from an established mechanism of validity and reliability checks performed by the data vendor. Antibiotic use data are derived from antibiotic orders; therefore, any drugs that were ordered and not administered to children would misclassify those children with respect to antibiotic use.

CONCLUSIONS

We found that the majority of patients admitted to children's hospitals were exposed to antibiotics. Individual hospitals varied significantly, however, in their use of antibiotic agents. Establishing benchmarks for antibiotic use will help to inform hospital and public policy aimed to treat children with known or presumed infections judiciously.

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