Use of Carbapenems, Polymyxins, and Tigecycline in United States Children's Hospitals, 2010–2014

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We characterized use of the carbapenems, polymyxins, and tigecycline in United States children's hospitals between 2010 and 2014. We found substantial variability in use across hospitals and overall decreased use over time. Most polymyxin and tigecycline use occurred in cystic fibrosis patients, and appendectomy was a common indication for carbapenem therapy.

Keywords. antibiotic stewardship; carbapenem; colistin; tigecycline.

The prevalence of infections caused by antibiotic-resistant Gram-negative organisms, including carbapenem-resistant Enterobacteriaceae, multidrug-resistant (MDR) Acinetobacter baumannii and Pseudomonas aeruginosa, and extended spectrum β-lactamase-producing Enterobacteriaceae, is increasing worldwide and represents a major public health threat [1–4]. The carbapenems are a mainstay of therapy for these highly drug-resistant infections, but increasing reports of carbapenem resistance threatens the future efficacy of these agents [4, 5]. Treatment options for carbapenem-resistant infections are extremely limited and include the polymyxins (polymyxin B and colistin) and tigecycline [5]. Collectively, these “reserved” antibiotics represent important antibiotic stewardship targets given the paucity of novel agents to treat resistant Gram-negative infections, especially in children; however, limited data exist on patterns of use in children to inform these potential stewardship interventions.

The aim of this study was to quantify and compare use of these reserved agents across US children's hospitals and over time and to identify clinical conditions associated with high utilization.

METHODS

Study Design and Data Source

Data were obtained from the Pediatric Health Information System (PHIS) database (Children's Hospital Association, Overland Park, KS), a clinical and administrative database containing inpatient and observation data from 48 children's hospitals in 38 states and the District of Columbia. Our analysis included 46 hospitals that contributed data during the study period.

Study Population and Definitions

Patients less than 21 years of age discharged between January 1, 2010 and December 31, 2014 who received at least 1 dose of a parenteral antibiotic were included. Our cohort was limited to those receiving parenteral antibiotics to characterize use of reserved agents among patients in whom parenteral antibiotic therapy was indicated.

Antibiotic Use

Reserved agents included carbapenems (imipenem-cilastatin, meropenem, doripenem, and ertapenem), polymyxins (polymyxin B and colistin [queried in the PHIS database as colistimethate sodium]), and tigecycline. Nonreserved broad-spectrum Gram-negative agents included ceftriaxone, ceftazidime, cefepime, ciprofloxacin, levofloxacin, moxifloxacin, piperacillin-tazobactam, and ticarcillin-clavulanate. Antibiotic use was quantified as days of therapy (DOT) per 1000 patient days. Days of therapy is the aggregate sum of all days of each antibiotic the patient received [6].

Clinical Conditions and High-Risk Cohort

Clinical conditions were identified using all patient-refined diagnosis-related group (APR-DRG) codes as well as the complex chronic conditions (CCC) based on International Classification of Diseases 9th Edition codes [7, 8]. The neonatal APR-DRGs (APR-DRG 580–640) were combined into a single neonatal clinical condition. Intensive care unit (ICU) level of care was defined as 2 or more consecutive days of mechanical ventilation or vasoactive medication (dopamine, epinephrine, norepinephrine, or dobutamine) or a single day of extracorporeal membrane oxygenation. “High-risk” patients were defined a priori as those with an APR-DRG code for malignancy, solid organ transplant, hematopoietic stem cell transplant, hematologic/immunologic condition, or those who required ICU level of care.
RESULTS

Demographic and Clinical Characteristics
During the 5-year study period, 1,618,885 admissions received at least 1 dose of a parenteral antibiotic, including 755,136 (47%) exposed to nonreserved broad-spectrum Gram-negative agents and 64,280 (4%) exposed to reserved agents. Of the 64,280 admissions, 60,518 (94%) received a carbapenem, 4,531 (7%) received a polymyxin, and 512 (1%) received tigecycline. Total DOT for all reserved agents was 550,645 days. Most DOT were accounted for by carbapenem use (94%, 516,837 days), whereas polymyxins and tigecycline accounted for 5% (28,043 days) and 1% (5,765 days), respectively. Approximately half of carbapenem DOT were accounted for by APR-DRG codes for neonatal care (11%), bone marrow transplant (9%), cystic fibrosis (9%), appendectomy (7%), tracheostomy with long-term mechanical ventilation with extensive procedure (4%), or major hematologic/immunologic diagnosis except sickle cell disease/coagulopathy (4%). Among patients undergoing appendectomy, meropenem was the most commonly used carbapenem (20,292 DOT, 59%), followed by ertapenem (13,049 DOT, 38%). Most polymyxin (60%) and tigecycline (50%) DOT occurred in patients with cystic fibrosis; bone marrow transplant patients accounted for 7% of tigecycline use, and no other condition accounted for more than 5% of DOT for either of these agents.

Variation in Use Across Hospitals
Reserved antibiotic use varied widely across centers (Figure 1a). To address potential differences in patient populations that may influence the risk of resistant Gram-negative infections and, therefore, the need (or perceived need) for reserved antibiotic therapy, comparisons of reserved antibiotic use across hospitals were then limited to children with high-risk conditions. Despite this stratification, use of reserved agents still varied substantially across hospitals with only 5 hospitals accounting for 24% of all DOT (Figure 1b). Finally, to compare use among high-utilizing conditions, we evaluated patterns of carbapenem use in patients undergoing appendectomy across centers and found significant variability: only 5 hospitals accounted for 73% of all DOT (Figure 1c). At these hospitals, less than 2% of patients undergoing appendectomy treated with a carbapenem required ICU care and over 95% had no CCC. Among cystic fibrosis patients, use of polymyxins and tigecycline was also highly variable with the top 5 utilizing institutions accounting for 39% and 46% of DOT, respectively.

Variation in Antibiotic Use Over Time
Over the 5-year study period, total use of reserved agents declined by 24% overall, driven primarily by a decrease in carbapenem and polymyxin use. In contrast, although tigecycline use remained very rare, use increased over the study period from 0.28 DOT/1000 patient days to 0.49 DOT/1000 patient days. Results were unchanged when the analysis was replicated including only hospitals that contributed data for the entire study period.
DISCUSSION

We found substantial variability in use of carbapenems, polymyxins, and tigecycline across US children’s hospitals despite restricting the analysis to a subset of patients with high-risk and high-utilizing conditions. Although differences in case mix among children admitted to freestanding children’s hospitals and within the selected diagnoses undoubtedly remain, the consistency of the variability in use across cohorts and the large sample size (which should help to provide a relatively similar case mix across hospitals over time) suggest that local antibiotic prescribing culture rather than patient differences drove differences in prescribing rates, a finding consistent with prior reports [9]. Although differences in prevalence of MDR organisms could also account for some of the observed variability, which was not assessed in the present study, such disparate rates of antibiotic resistance across freestanding children’s hospitals have not been reported. Furthermore, carbapenem utilization among patients undergoing appendectomy, a population largely without comorbid medical conditions or need for ICU care and therefore presumably at low risk of MDR organism acquisition, was also extremely variable with 73% of use concentrated in just 5 geographically diverse institutions. Therefore, this represents a potential target for stewardship interventions, especially in light of recent comparative effectiveness data suggesting no difference in outcomes for patients undergoing appendectomy treated with narrower versus extended-spectrum antibiotics [10].

Despite high utilization in certain conditions and centers, use of reserved agents appeared to decline over time both in the overall cohort as well as in high-risk patients, consistent with existing literature [11]. It is interesting to note that use of carbapenems appeared to increase until 2007, followed by a decline in use of reserved agents between 2007 and 2014 [11, 12]. The reason for this reduction is unclear and appears to be at odds with reports of increasing prevalence of antibiotic-resistant organisms, but it may be related to (1) implementation of antimicrobial stewardship programs, which were recommended by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America in 2007, resulting in more judicious use of these agents for non-MDR Gram-negative infections, and (2) a relative lack of emergence of MDR organisms at freestanding children’s hospitals compared with centers that care primarily for adults [2, 4, 13].

Our study has several limitations. We used daily billing data to assess antibiotic use rather than actual drug administrations, potentially overestimating the proportion of patients receiving reserved agents as well as DOT received. This should be non-differential across hospitals, clinical conditions, and time, and, therefore, not a significant source of bias. Our analyses also included only parenteral antibiotics, so we cannot comment on use of antibiotics administered via other routes; this may be of particular relevance in cystic fibrosis patients in whom nebulized colistin use could have replaced parenteral colistin at apparently low-utilizing centers. Patient conditions were also classified by APR-DRG codes, but just a single code is assigned for the entire hospital stay and therefore may not reflect the true complexity of the admission or indication for an antibiotic. Furthermore, PHIS does not contain microbiology data, so we were unable to determine the types of infections or resistance profiles of any identified bacterial infection. Finally, missing data could represent an additional source of bias, although we have repeated our analyses limited only to hospitals submitting data for the whole study period and reached similar conclusions, making this unlikely.

CONCLUSIONS

In conclusion, carbapenem, polymyxin, and tigecycline use primarily occurs in patients with a select group of diagnoses and varies significantly across US children’s hospitals. These diagnoses, especially appendicitis, represent possible important targets for antimicrobial stewardship efforts as well as further studies evaluating the comparative effectiveness of these reserved agents versus narrower spectrum alternatives.

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