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MAJOR ARTICLE

Antibiotic Indications and Appropriateness in the Pediatric Intensive Care Unit: A 10-Center Point Prevalence Study

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Background. Antibiotics are prescribed to most pediatric intensive care unit (PICU) patients, but data describing indications and appropriateness of antibiotic orders in this population are lacking.

Methods. We performed a multicenter point prevalence study that included children admitted to 10 geographically diverse PICUs over 4 study days in 2019. Antibiotic orders were reviewed for indication, and appropriateness was assessed using a standardized rubric.

Results. Of 1462 patients admitted to participating PICUs, 843 (58%) had at least 1 antibiotic order. A total of 1277 antibiotic orders were reviewed. Common indications were empiric therapy for suspected bacterial infections without sepsis or septic shock (260 orders, 21%), nonoperative prophylaxis (164 orders, 13%), empiric therapy for sepsis or septic shock (155 orders, 12%), community-acquired pneumonia (CAP; 118 orders, 9%), and post-operative prophylaxis (94 orders, 8%). Appropriateness was assessed for 985 orders for which an evidence-based rubric for appropriateness could be created. Of these, 331 (34%) were classified as inappropriate. Indications with the most orders classified as inappropriate were empiric therapy for suspected bacterial infection without sepsis or septic shock (78 orders, 24%), sepsis or septic shock (55 orders, 17%), CAP (51 orders, 15%), ventilator-associated infections (47 orders, 14%), and post-operative prophylaxis (44 orders, 14%). The proportion of antibiotics classified as inappropriate varied across institutions (range, 19%–43%).

Conclusions. Most PICU patients receive antibiotics. Based on our study, we estimate that one-third of antibiotic orders are inappropriate. Improved antibiotic stewardship and research focused on strategies to optimize antibiotic use in critically ill children are needed.

Keywords. pediatric intensive care unit; antimicrobial stewardship; sepsis; antibiotic.

Children admitted to the pediatric intensive care unit (PICU) are a highly complex and vulnerable patient population who frequently experience serious bacterial infections, either as the primary reason for PICU admission or as a complication of hospitalization for critical illness [1–4]. Further, nonspecific signs of systemic inflammation are common among critically ill children and often prompt initiation of broad-spectrum antimicrobials, an approach driven in part by the deleterious impacts of delayed antimicrobial therapy in patients with bacterial septic shock [5–7]. Collectively, these factors contribute to high utilization of broad-spectrum antimicrobials in the PICU, with prior studies demonstrating that 56%–80% of children hospitalized in the PICU receive 1 or more antibiotics during their stay [8–12].

While undoubtedly beneficial for patients with bacterial infections, antibiotics also carry a risk of adverse drug events, acute kidney injury, or *Clostridioides difficile* infection and contribute to the burgeoning issue of antimicrobial resistance [13–17]. These potential harms are amplified in the PICU, as critically ill children are at increased risk for infections due to antimicrobial resistant organisms, may be prone to developing serious adverse events from coexisting organ system failures (eg, preexisting acute kidney injury exacerbated by vancomycin administration), and are often on numerous medications, heightening the potential risk of drug interactions (eg, interactions between ciprofloxacin and other QTc prolonging medications) [18, 19]. Optimized antibiotic stewardship approaches

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that integrate the need for urgent antimicrobials in a population at high risk for septic shock, the challenge of differentiating true infections from noninfectious mimics, and the high risk of preventable harm from unnecessary antibiotic exposure are therefore critical.

There is significant hospital-level variation in antibiotic use across PICUs [20]. Single-center studies have reported estimates of inappropriate antibiotic use in the PICU ranging from 0% to 61% [11, 12, 21]. A large multicenter cohort study of hospitalized children in the United States estimated that approximately 34% of antibiotics prescribed to children hospitalized in the PICU were suboptimal [22]. Our aim in this multicenter study was to build on this prior work by comprehensively characterizing antibiotic indications and systematically assessing the appropriateness of antibiotics prescribed to critically ill children to define targets for improved antimicrobial stewardship in the PICU.

METHODS

Study Design and Setting

This cross-sectional, point prevalence study was conducted in the PICUs of 10 tertiary care, geographically diverse children's hospitals in the United States. All participating centers have antimicrobial stewardship programs. The participating PICUs ranged in size from 18 to 84 beds. Data were collected on 4 weekdays during specified 2-week periods between January 2019 and June 2019. Institutional review board approval was obtained at each institution.

Study Population

All PICU patients aged 0–20 years with 1 or more nontopical antibiotics ordered at 8:00 AM on each study day were included. Within this overall study population, patients were further classified as having received broad-spectrum antibiotics if they received at least 1 of the following: third- or fourth-generation cephalosporin, fluoroquinolone, carbapenem, piperacillin-tazobactam, ceftazidime-avibactam, vancomycin, linezolid, or daptomycin. Patients with only antifungal or antiviral medication orders were excluded.

Data Collection

Data were collected by attending or fellow physicians in pediatric critical care and/or infectious diseases using a standardized data collection form through manual review of clinical documentation available in the electronic health record. Data were entered into a Research Electronic Data Capture database hosted at Children's Hospital of Philadelphia. Approximately 100 rules for checking data quality were integrated, and potential discrepancies were resolved with site principal investigators. Patient-level variables included clinical and demographic data. Because each patient may have had active orders for more than 1 antibiotic, antibiotic indication and appropriateness were assessed for each individual order.

Defining Antibiotic Indication

Antibiotic indication was determined based on clinical documentation (including PICU progress notes, consultant notes, and orders) and reflected the use intended by the ordering clinician. Indications were grouped into 6 categories: prophylaxis, defined as an antibiotic prescribed to prevent an infection in a patient without a suspected or definite infection; empiric therapy, defined as an antibiotic prescribed for a suspected infection for which a diagnosis of a definite infection has not yet been made by the clinician; treatment of a clinician-diagnosed infection; a noninfectious condition; cystic fibrosis or bronchiectasis exacerbation; or febrile neutropenia (eg, while awaiting neutrophil count recovery). Antibiotics prescribed for prophylaxis were subcategorized into those prescribed for post-operative prophylaxis and non–-post-operative prophylaxis. Antibiotics prescribed for empiric therapy were subcategorized into those ordered for suspected bacterial infections without sepsis-associated organ dysfunction or shock and those ordered for suspected bacterial infection with sepsis-associated organ dysfunction or septic shock, as defined by published criteria [23]. All clinician-diagnosed infections were reported by source. Nonsystemic antibiotics, including inhaled, intraventricular, and intravesical antibiotics, were considered separately as one group.

Defining Antibiotic Appropriateness

Antibiotic appropriateness was assessed using a standardized indication-specific rubric based on national or international guidelines, published literature, and expert consensus (Supplementary Table 1). Investigators were also permitted to enter "other" reasons for inappropriate antibiotic prescribing as well as to "disagree" with the established rubric. These responses were independently evaluated by 2 investigators (K. C. and J. S. G.) and reconciled with the site principal investigator. All orders for post-operative prophylaxis, empiric therapy, and clinician-diagnosed infections were assessed for appropriateness. Antibiotic orders for all other indications were not assessed for appropriateness, as decisions for using these antibiotics are generally not made by intensivists and/or guidelines informing optimal use are not available (Supplementary Table 2). Inappropriate antibiotic orders for clinician-diagnosed infections were further subclassified as "definitely" or "likely" inappropriate; likely inappropriate orders are those where there is greater subjectivity in assessing appropriateness (Supplementary Table 1).

Data Analyses

We analyzed antibiotic choices and indication using standard descriptive statistics, using frequencies and proportions. In the primary analysis, all definite or likely inappropriate

Table 1. Clinical and Demographic Characteristics of Pediatric Intensive Care Unit Patients Who Received Antibiotics

Characteristic	Any Antibiotic, n (%) (Total N = 843)	Broad-Spectrum Antibiotic,[a] n (%) (Total N = 494)
Age, median (interquartile range), months	47 (13–149)	72 (13–162)
Male sex	448 (53)	250 (51)
Race		
White	490 (58)	302 (61)
Black	152 (18)	82 (17)
Asian	46 (5)	29 (6)
American Indian/Alaskan Native	6 (1)	2 (<1)
Native Hawaiian/Pacific Islander	3 (<1)	3 (<1)
Other/Mixed Race	61 (7)	30 (6)
Not reported	85 (10)	46 (9)
Ethnicity		
Hispanic or Latino	142 (17)	86 (17)
Not Hispanic or Latino	605 (72)	354 (72)
Not reported	95 (11)	53 (11)
Institution		
1	173 (21)	110 (22)
2	144 (17)	73 (15)
3	113 (13)	71 (14)
4	73 (9)	44 (9)
5	69 (8)	35 (7)
6	69 (8)	45 (9)
7	67 (8)	37 (7)
8	63 (7)	35 (7)
9	39 (5)	25 (5)
10	34 (4)	21 (4)
Study day		
1	211 (25)	127 (26)
2	197 (23)	127 (26)
3	226 (27)	128 (26)
4	209 (25)	112 (23)
Comorbid medical conditions		
Previously healthy	173 (21)	108 (22)
Immunocompromised[b]	199 (24)	116 (23)
Respiratory		
Chronic respiratory failure[c]	172 (20)	82 (17)
Chronic respiratory insufficiency[d]	74 (9)	39 (8)
Cardiac		
Pulmonary hypertension	77 (9)	39 (8)
Congenital heart disease	105 (12)	51 (10)
Neurologic		
Static encephalopathy/severe developmental delay[e]	168 (20)	100 (20)
Seizure disorder	140 (17)	81 (16)
Neuromuscular disease	58 (7)	33 (7)
Other neurologic condition	31 (4)	20 (4)
Renal		
Chronic dialysis dependence or chronic kidney disease	29 (3)	15 (3)
Neurogenic bladder or abnormal genitourinary tract anatomy	46 (5)	30 (6)
Prematurity (<32 weeks' gestation)	80 (9)	45 (9)
Genetic or metabolic syndrome	76 (9)	45 (9)
Endocrine disease	13 (2)	11 (2)
Hematologic disease	19 (2)	9 (2)
Hepatic disease	7 (1)	5 (1)
Nonhepatic gastrointestinal disease	29 (3)	22 (4)
Other comorbidity[f]	12 (2)	2 (<1)
Invasive medical devices (within 7 days)		
None	143 (17)	76 (15)
Central venous catheter	461 (55)	310 (63)
Arterial line	231 (27)	163 (33)
Endotracheal tube	328 (39)	215 (44)
Tracheostomy	209 (25)	107 (22)
Foley catheter	211 (25)	142 (29)
Externalized ventricular drain	42 (5)	29 (6)
Intensive care unit therapies (within 7 days)		
None	139 (16)	77 (16)
Invasive mechanical ventilation	532 (63)	318 (64)
Noninvasive mechanical ventilation	174 (21)	96 (19)
Vasoactive infusion	185 (22)	139 (28)
Extracorporeal membrane oxygenation	17 (2)	14 (3)
Inhaled nitric oxide	31 (4)	27 (6)
Penicillin or cephalosporin allergy	68 (8)	41 (8)
Severe penicillin or cephalosporin allergy[g]	4 (<1)	3 (<1)

[a]Includes third- or fourth-generation cephalosporin, fluoroquinolone, carbapenem, piperacillin-tazobactam, ceftazidime-avibactam, vancomycin, linezolid, or daptomycin.

[b]Includes patients who have undergone a bone marrow transplant, solid organ transplant, are being actively treated for a malignancy, or are receiving systemic immunosuppression with tacrolimus, sirolimus, oral or subcutaneous methotrexate ≥5 mg, prednisone 2 mg/kg/day or ≥ 20 mg daily for >2 weeks, cyclophosphamide, rituximab, mycophenolate mofetil, azathioprine, anakinra, infliximab, etanercept, adalimumab, or any other monoclonal antibody or any tumor necrosis factor-alpha inhibitor when taken for nonmalignant, nontransplant condition.

[c]Includes patients with tracheostomies requiring long-term mechanical ventilation for all or part of the day prior to admission.

[d]Includes patients requiring noninvasive mechanical ventilation (continuous positive airway pressure or bilevel positive airway pressure) for all or part of the day prior to admission.

[e]Impaired consciousness severe enough to result in patients being nonverbal or nonambulatory.

[f]Lymphatic disorder/lymphangectasia (6), cardiomyopathy (4), other/not specified (2).

[g]Includes anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms.

antibiotic use was classified as inappropriate. As a secondary analysis, we report only the frequency and proportions of antibiotics classified as definitely inappropriate.

RESULTS

Patient Demographic and Clinical Characteristics

Among the 1462 patients admitted to the 10 PICUs over the 4 study days, 843 patients (58%) were prescribed at least 1 antibiotic and 494 (34%) received at least 1 broad-spectrum antibiotic. A total of 311 (37%) received 2 or more antibiotics. Most patients who received antibiotics (670 of 843, 79%) had 1 or more comorbid medical conditions; chronic respiratory failure and static encephalopathy/severe developmental delay were most common, each occurring in 20% of patients. Almost two-thirds (63%) of patients received mechanical ventilation within

Table 2. Indications for Antibiotic Orders in Pediatric Intensive Care Unit Patients

Indication Category	Subcategory	n (%) Total N = 1277
Prophylaxis: antibiotic ordered to prevent an infection when no suspected or documented infection for which this antibiotic ordered was present Total antibiotic orders for prophylaxis = 258/1277 (20%)	Post-operative	94 (7)
	Non–post-operative[a]	164 (13)
Empiric: antibiotic ordered for a suspected infection in which a diagnosis of a definite infection had not yet been made by the clinician Total antibiotic orders for empiric therapy = 415/1277 (32%)	Suspected bacterial infection (no sepsis or septic shock)	260 (20)
	Specific source suspected	188
	No specific source suspected	72
	Sepsis-associated organ dysfunction or septic shock	155 (12)
	Specific source suspected	104
	No specific source suspected	51
Clinician-diagnosed infection Total orders for treatment of a clinician-diagnosed infection = 476/1277 (37%)	Bacteremia (central line–associated bloodstream infection or noncatheter-associated)	47 (4)
	Meningitis or ventriculitis	28 (2)
	Community-acquired pneumonia	123 (10)
	Hospital-acquired pneumonia	34 (3)
	Ventilator-associated infection (includes pneumonia or tracheitis)	86 (7)
	Intraabdominal infection	33 (3)
	Urinary tract infection (catheter-associated urinary tract infection or noncatheter-associated)	39 (3)
	Skin or soft tissue infection	23 (20)
	Culture-negative sepsis	5 (<1)
	Other	58 (12)
	Clostridioides difficile	18
	Head, eye, ear, nose, or throat infection	25
	Home medication	7
	Other respiratory	4
	Donor-derived infection	2
	Endovascular infection	2
Noninfectious condition Total orders for noninfectious condition = 76/1277 (6%)	Antiinflammatory	29 (2)
	Gastrointestinal motility	33 (3)
	Small bowel bacterial overgrowth	10 (<1)
	Other	4 (<1)
Cystic fibrosis or bronchiectasis exacerbation Total orders for cystic fibrosis or bronchiectasis exacerbation = 5/1277 (<1%)	No subcategories	5 (<1)
Febrile neutropenia (secondary prophylaxis while awaiting count recovery) Total orders for febrile neutropenia = 18/1277 (1%)	No subcategories	18 (1)
Nonsystemic route Total orders administered by a nonsystemic route = 20/1277 (2%)	Inhaled	16 (1)
	Intraventricular	2 (<1)
	Intravesical	2 (<1)
	Intraperitoneal	0 (0)
Cannot determine Total orders for which an indication could not be determined = 9/1277 (<1%)	No subcategories	9 (<1)

[a]Nonoperative prophylaxis includes prophylaxis for opportunistic infections in immunocompromised hosts, urinary tract infection prophylaxis, endocarditis prophylaxis, and extracorporeal membrane oxygenation prophylaxis.

7 days of the study day, and 22% received vasoactive infusions (Table 1).

Antibiotic Choice

Of the 1277 antibiotic orders, 897 (70%) were administered intravenously, 360 (28%) enterally, and 20 (2%) by the intraventricular, intravesicular, or inhaled routes combined. The most common antibiotic orders were intravenous vancomycin (152, 12%), ceftriaxone (148, 12%), cefepime (146, 12%), trimethoprim-sulfamethoxazole (134, 11%), and metronidazole (65, 5%). Across the 10 institutions, at least 3 of these 5 overall top antibiotics appeared in each institution's top 5 antibiotics, though there was substantial variability in the other top antibiotics (Supplementary Table 3*A*).

Antibiotic Indications

Treatment for clinician-diagnosed infections accounted for most antibiotic orders (476, 38%), followed by empiric therapy for suspected bacterial infections (415, 33%), nonoperative prophylaxis (164, 13%), and post-operative prophylaxis (94 orders, 7%). Less common indications for antibiotic orders included noninfectious indications, including antiinflammatory effect and gastrointestinal motility (76, 6%), febrile neutropenia (18, 1%), and cystic fibrosis exacerbation (5, 0.4%). We were unable to determine indication for 9 orders (<1%; Table 2).

Within these broad indications, antibiotic orders for empiric therapy for suspected bacterial infections without sepsis-associated organ dysfunction or shock (260, 21%), prophylaxis for nonoperative indications (164, 13%), empiric therapy for suspected bacterial infection with sepsis-associated organ dysfunction or septic shock (155, 12%), community-acquired pneumonia (CAP; 118, 9%), and post-operative prophylaxis (94, 8%) were most common. Among antibiotic orders for empiric therapy for suspected bacterial infection, a specific source of infection was suspected in 70% (Table 2). Across the 10 institutions, at least 3 of the 5 overall top indications appeared in each institution's top 5 indications, though there was substantial variability regarding the other top indications (Supplementary Table 3*B*).

Antibiotic Appropriateness

Of the 843 patients who received antibiotics during the study, 283 (34%) received 1 or more antibiotics classified as inappropriate. Of the 1277 individual antibiotic orders, 985 (77%) were assessed for appropriateness using our standardized rubric; the majority of the remaining 292 orders were antibiotics administered for nonoperative prophylaxis or noninfectious indications (Supplementary Table 2). A total of 331 (34%) antibiotic orders assessed were classified as inappropriate. The antibiotics accounting for the greatest proportion of all inappropriate orders were cefepime (54, 16%), ceftriaxone (34, 11%), vancomycin (28, 8%), meropenem (25, 8%), and piperacillin-tazobactam (22, 7%; Figure 1*A*). The indications accounting for the greatest proportion of all inappropriate antibiotic orders were inappropriate empiric therapy for suspected bacterial infections without organ dysfunction (78 of 331, 24%), empiric therapy for suspected bacterial infection with sepsis-associated organ dysfunction or septic shock (55 of 331, 17%), CAP (51 of 331, 15%), ventilator-associated infections (VAI) including ventilator-associated pneumonia (VAP) and ventilator-associated tracheitis (47 of 331, 14%), and post-operative prophylaxis (44 of 331, 13%; Figure 1*B*).

Common reasons for classifying antibiotic orders as inappropriate include prolonged empiric therapy (78, 24%), antibiotics ordered for a clinician-diagnosed infection where evidence of a bacterial infection was lacking (70, 21%), overly broad-spectrum therapy for a clinician-diagnosed infection (58, 18%), prolonged post-operative prophylaxis (41, 12%), and excessive duration of therapy for a clinician-diagnosed infection (36, 11%; Tables 3 and 4).

In a secondary analysis limited to antibiotic orders classified as definitely inappropriate (265 of 331 total inappropriate orders, 80%), hospital-acquired pneumonia (HAP), VAI, and CAP remained the clinician-diagnosed infections accounting for the greatest number of inappropriate orders. The most common reasons antibiotic orders were classified as inappropriate were therapy that was too broad, duration of therapy that was too long, and suboptimal route of administration (Supplementary Table 4).

Institutional Variation

The proportion of patients who received any antibiotics varied across institutions (range, 47%–62%), as did the proportion of patients receiving broad-spectrum antibiotics (range, 28%–39%). There was variability in the proportion of antibiotic orders classified as inappropriate, ranging from 19% to 43% (Figure 2).

DISCUSSION

In this multicenter study, we determined that 58% of children hospitalized in tertiary care US PICUs received antibiotics, with empiric therapy for suspected bacterial infections and treatment of clinician-diagnosed respiratory infections being the most common indications for antibiotic use. More than one-third of patients received 1 or more antibiotics classified as inappropriate, and 34% of all antibiotic orders assessed for appropriateness were classified as inappropriate. Prolonged empiric antibiotic therapy for suspected bacterial infection with or without shock, antibiotics prescribed absent clinical evidence of a bacterial infection (particularly antibiotics ordered for respiratory infections), unnecessarily broad antibiotic therapy, antibiotics ordered for excessive durations, and prolonged post-operative prophylaxis were common reasons antibiotic orders were classified as inappropriate. Collectively, these findings identify targets for improved antibiotic stewardship in critically ill children and identify future research needs in this area.

To date, studies evaluating antibiotic appropriateness in the PICU consist primarily of single-center reports and studies conducted outside of the US, and these reports estimate that 18%–61% of patients receive inappropriate antibiotics [11, 12, 21, 24, 25]. In the largest US study performed to date that evaluated antibiotic use in hospitalized children, 34% of nonneonatal ICU patients received at least 1 inappropriate antibiotic [22]. While granularity of antibiotic indications and the reasons for inappropriate use were not provided specifically for the PICU patients in this report, the consistency of the overall estimate across these 2 large studies supports the robustness of this

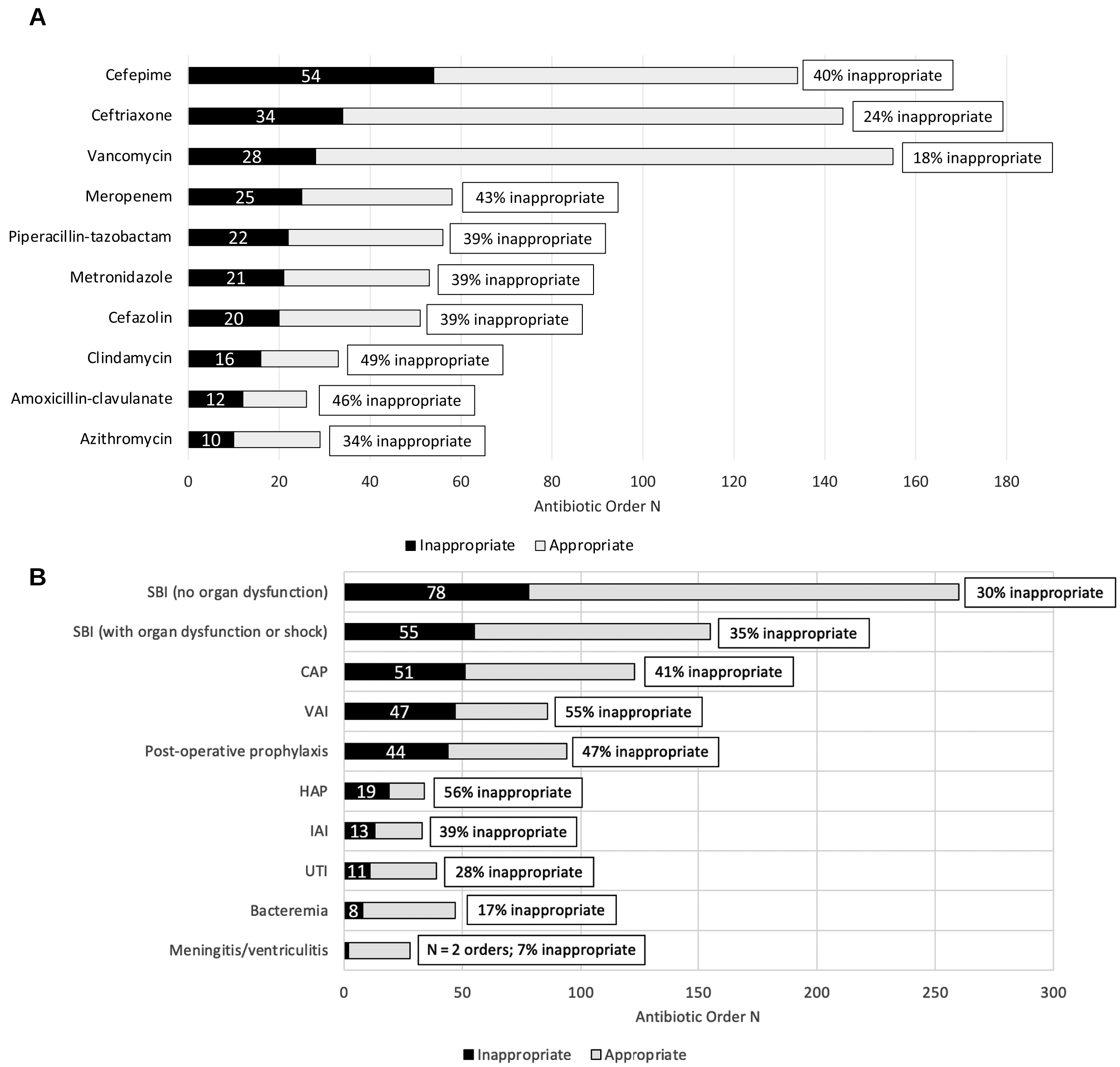

Figure 1. *A,* Top inappropriate antibiotic orders by drug. The total bar is the number of antibiotic orders that were reviewed for appropriateness, sorted by antibiotic. The black stacked bar indicates antibiotic orders classified as inappropriate. The gray portion of the stacked bar indicates the antibiotic orders classified as appropriate. The numbers on each bar indicate the total number of antibiotic orders. *B,* Top inappropriate antibiotic order indications. The total bar is the number of antibiotics that were reviewed for appropriateness, sorted by indication. The black stacked bar indicates antibiotic orders classified as inappropriate. The gray portion of the stacked bar indicates the antibiotic orders classified as appropriate. The numbers on each bar indicate the total number of antibiotic orders. Abbreviations: CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; IAI, intraabdominal infection; SBI, suspected bacterial infection; UTI, urinary tract infection; VAI, ventilator-associated infection.

estimate in quantifying the magnitude of inappropriate antibiotic use in US PICUs.

Our study builds on this prior work and introduces several novel findings. First, empiric therapy for suspected bacterial infections, with or without sepsis-associated organ dysfunction or septic shock, was the most common indication for antibiotic orders in the PICU. Efforts to improve antibiotic prescribing in the PICU must therefore include efforts to optimize empiric therapy, particularly given that many stewardship programs use prospective audit with feedback, where reviews may not occur until 48–72 hours after antibiotics are initiated [26]. Such efforts should target both the urgency of empiric antibiotic administration and the empiric antibiotic choice. National guidelines, regulatory mandates, and quality improvement collaboratives have appropriately emphasized the need for emergent broad-spectrum antibiotics administered within 1 hour for patients with septic shock given associations between prolonged time to antibiotics and deleterious clinical outcomes

Table 3. Inappropriate Antibiotic Orders and Reasons for Inappropriate Classification by Indication Category

Category	n (%), Total Inappropriate Orders = 331
Prophylaxis[a]	44 (13)
Post-operative prophylaxis >24 hours (clean/clean contaminated procedure)	41 (12)
Post-operative antibiotic choice not aligned with national guidelines (allergy or **multidrug-resistant organism** excluded)	3 (1)
Empiric therapy[a]	133 (40)
Empiric therapy given ≥4 days without a clinician-diagnosed infection defined, unless pending surgical procedure or microbiologic or other diagnostic test	78 (24)
Antipseudomonal beta-lactam ordered for a community-onset infection,[b] absent an invasive device or residence in a long-term care facility	25 (8)
Antibiotic choice not compliant with local guidelines (absent an allergy, **multidrug-resistant organism** history, or treatment failure)	23 (7)
Antibiotic choice noncompliant with Surviving Sepsis Campaign guidelines and administered for sepsis	6 (2)
Antibiotic orders for **community-acquired pneumonia** with no radiographic infiltrate *and* no need for new or escalated respiratory support	6 (2)
Antibiotic orders for **urinary tract infection** with no clinical symptoms, pyuria, or nitrites	2 (<1)
Clinician-diagnosed infection[a,c]	154 (47)
Lack of supporting clinical evidence of bacterial infection	70 (21)
Too broad	58 (18)
Inappropriate duration	36 (11)
Inappropriate route	27 (8)
Overlapping coverage	9 (3)
Too narrow	3 (1)

[a]Antibiotic orders may be classified as inappropriate for multiple reasons. Therefore, the column totals and percentages will exceed 331 (100%) inappropriate orders.

[b]Community-onset infection was defined as an infection that was present upon admission or occurred within 48 hours of hospitalization. Patients with invasive devices or those who reside in long-term care facilities were excluded from this definition.

[c]See Supplementary Table 1 for detailed criteria for assessing appropriateness of antibiotic orders for clinician-diagnosed infection.

[7, 27]. However, for less severely ill patients, this association is weak or absent, such that overemphasis on emergent broad-spectrum antibiotic administration for all patients risks overtreatment of patients in whom a focal source of infection or a noninfectious condition could have been identified prior to antibiotic administration [5, 6, 28]. In our cohort, almost two-thirds of patients who received empiric antibiotics did not have septic shock or sepsis-associated organ dysfunction, highlighting that this strategy may be feasible in many cases. Further, overuse of empiric anti–methicillin-resistant *Staphylococcus aureus* and anti-pseudomonal antibiotics in patients unlikely to be infected with these resistant organisms (eg, patients with community-onset sepsis) is supported by both the current study and published literature [29–31]. While improved clinical prediction rules and rapid molecular diagnostic tests hold promise for tailoring empiric antibiotic choices to patient risk of multidrug-resistant organisms, quality improvement initiatives that target reductions in empiric vancomycin administration in the PICU based on readily available clinical information have been shown to be both safe and effective, highlighting this current potential opportunity for improved stewardship [30, 31].

Second, inappropriately prolonged durations of empiric antibiotic therapy accounted for almost one-quarter of inappropriate antibiotic use, consistent with published literature and demonstrating that once initiated, antibiotics are often not deescalated or discontinued in a timely fashion [32, 33]. This underscores the importance of an appropriate infectious evaluation at the time of antibiotic initiation to inform subsequent decision making, as well as the need for reassessment after 48–72 hours of antibiotic therapy [34]. However, there are significant knowledge gaps regarding current deescalation strategies that warrant further study in the critical care setting, including the optimal approach for implementing a prospective audit with feedback, the impact of clinician-driven antibiotic time-outs, and the role for rapid molecular diagnostic testing and biomarkers.

Third, almost 50% of antibiotics ordered for post-operative prophylaxis were classified as inappropriate, the majority of which were classified as inappropriate due to being administered for >24 hours after surgery. This estimate of inappropriate antibiotic use is conservative, as the Surgical Infection Society recommends against any antibiotic administration after skin closure [35]. Given these guideline recommendations and published data quantifying the additive risk of antibiotic adverse events with each additional day of unnecessary antibiotics following surgery, reducing duration of post-operative antibiotics should be a shared priority of intensivists, surgeons, and antimicrobial stewardship programs [36].

Finally, respiratory infections represented common indications for antibiotics, but evidence supporting a diagnosis of bacterial infection was lacking in up to 28%, while overly broad and excessively long treatment durations occurred in nearly 20% of HAP and VAP cases. Undoubtedly, the lack of a "gold standard" for diagnosing bacterial pneumonia hampers both individual clinical decision making and stewardship efforts in this area, highlighting the need for improved strategies for diagnosing these common conditions in the PICU. Nevertheless, stewardship interventions that are focused on optimizing the duration of antibiotics for VAP and HAP, with 7 days of therapy recommended by the 2016 Infectious Diseases Society of America /American Thoracic Society guidelines and supported by the results of randomized trials, represent an actionable target based on our results [37–39].

Despite these strengths, our work is subject to several limitations. First, assessment of antibiotic appropriateness is inherently subjective, particularly given that this assessment was performed retrospectively and by different individuals at each

Table 4. Reasons for Inappropriate Antibiotic Classification Among Patients Being Treated for Clinician-Diagnosed Infections

Indication	Total Orders for Indication, N	Inappropriate Orders, n (%)	Too Narrow, n (%)	Too Broad[a], n (%)	Overlapping Coverage, n (%)	Inappropriate Duration, n (%)	No Infection, n (%)	Suboptimal Route, n (%)
Bacteremia	47	8 (17)	0	6 (13)	2 (4)	4 (9)	2 (4)	0
Meningitis/ventriculitis	28	2 (7)	0	2 (7)	0	0	0	0
Community-acquired pneumonia	123	51 (41)	0	18 (15)	2 (2)	2 (2)	32 (26)	10 (8)
Hospital-acquired pneumonia	34	19 (56)	1 (3)	6 (18)	0	7 (21)	7 (21)	6 (18)
Ventilator-associated infection	86	47 (55)	2 (2)	16 (19)	1 (1)	14 (16)	24 (28)	8 (9)
Intraabdominal infection	33	13 (39)	0	3 (9)	4 (12)	8 (24)	1 (3)	0
Urinary tract infection	39	11 (28)	0	7 (18)	0	1 (3)	2 (5)	2 (5)
Skin or soft tissue infection	23	1 (4)	0	0	0	0	0	1 (4)
Culture-negative sepsis	5	2 (40)	0	0	0	0	2 (40)	0
Other	58	NA	NA	NA	NA	NA	NA	NA
Total[b]	476	154 (32)	3 (<1)	58 (12)	9 (2)	36 (8)	70 (15)	27 (6)

[a]Of the N orders classified as inappropriate due to therapy that is too broad, 2 orders for each community-acquired pneumonia, hospital-acquired pneumonia, and ventilator-associated infection were classified as inappropriate anti–methicillin-resistant *Staphylococcus aureus* therapy.

[b]Antibiotic orders may be classified as inappropriate for multiple reasons. Therefore, the row totals and percentages classified as inappropriate for each reason will exceed 154 inappropriate orders.

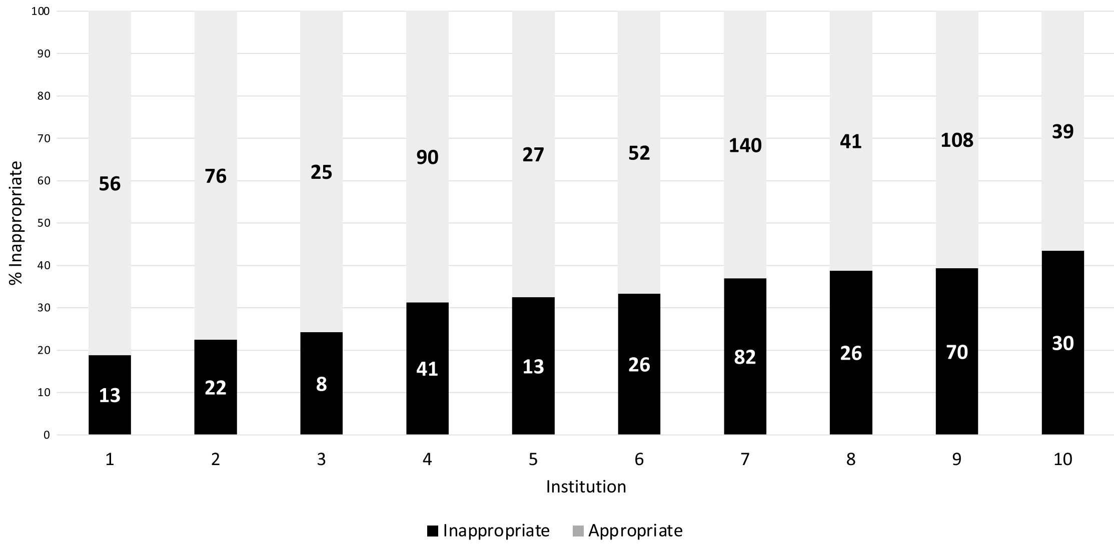

Figure 2. Variation in inappropriate antibiotic orders by institution. The black portion of the stacked bar indicates the proportion of antibiotic orders classified as inappropriate. The gray portion of the stacked bar indicates the proportion of antibiotic orders classified as appropriate. The numbers on each bar indicate the total number of antibiotic orders.

site. We sought to mitigate this by using a standardized rubric for assessing appropriateness, rather than allowing individuals to classify antibiotic orders as appropriate or inappropriate based on their own judgment. Assessing the appropriateness of antibiotic use for CAP, HAP, and VAI is particularly vulnerable to this limitation given the lack of a diagnostic gold standard for these infections. Second, while our assessment tool was based on available evidence-based guidelines, guidelines were not available for all scenarios encountered in the PICU and were often not specific to children. We were therefore permissive in classifying scenarios where evidence was weak or lacking as "appropriate" antibiotic use in the rubric, such that we may have underestimated inappropriate antibiotic use for some conditions. An example of this is empiric vancomycin use, which was classified as appropriate in all cases if administered for fewer than 4 calendar days. Third, our assessment spanned 4 days in 10 tertiary care PICUs, the majority of which were medical–surgical ICUs without cardiac surgical patients. Generalizability of our findings to smaller centers, where case mix may differ, is therefore unknown. However, our findings are strengthened given the geographic diversity of the PICUs, diversity in bed size, and given that 2 of the 10 PICUs did care for cardiac surgical patients. Finally, this study was performed in 2019, prior to the coronavirus disease 2019 pandemic. While this is a potential limitation, these prepandemic data and stewardship targets are arguably more reflective of the current case mix than 2020 or 2021 data given the changes in PICU case mix and decreases in PICU admissions during the pandemic [40].

Our study, which is the largest to date focused on antibiotic use in the PICU setting, demonstrated that more than one-third of critically ill children receive inappropriate antimicrobials. Tailoring empiric antibiotic choices, deescalating antibiotics when no bacterial infection has been identified, limiting the duration of post-operative antibiotics, and ensuring antibiotic durations are aligned with national guidelines represent actionable stewardship targets in this population. Future research that is focused on improving diagnostic modalities to differentiate bacterial infections from viral infections or noninfectious mimics, developing clinical prediction rules to more appropriately risk-stratify patients with regard to infections with antibiotic-resistant bacteria, and evaluating optimal implementation of evidence-based practices in the PICU setting are key opportunities for future research.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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