SUPPLEMENT ARTICLE

Assessing Appropriateness of Antimicrobial Therapy: In the Eye of the Interpreter

Daryl D. DePestel,[1] Edward H. Eiland III,[2,a] Katherine Lusardi,[3] Christopher J. Destache,[4] Renée-Claude Mercier,[5] Patrick M. McDaneld,[1,6,b] Kenneth C. Lamp,[1] Thomas J. Chung,[1] and Elizabeth D. Hermsen[1,7]

[1]Global Medical Affairs, Cubist Pharmaceuticals, Lexington, Massachusetts; [2]Department of Pharmacy, Huntsville Hospital, Alabama; [3]Department of Pharmacy, University of Arkansas for Medical Sciences Medical Center, Little Rock; [4]Creighton University School of Pharmacy and Health Professions, Omaha, Nebraska; [5]College of Pharmacy, University of New Mexico, Albuquerque; [6]Department of Pharmacy Practice, Massachusetts College of Pharmacy and Health Sciences, Worcester/Manchester; and [7]Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, Omaha

To address the increase of drug-resistant bacteria and widespread inappropriate use of antimicrobials, many healthcare institutions have implemented antimicrobial stewardship programs to promote appropriate use of antimicrobials and optimize patient outcomes. However, a consensus definition of appropriate use is lacking. We conducted a multicenter observational study to compare 4 definitions of appropriateness—a study site–specific definition, use supported by susceptibility data, use supported by electronic drug information resources (Clinical Pharmacology/Micromedex), or study site principal investigator (PI) opinion—among patients receiving 1 or more of 13 identified antimicrobials. Data were collected for 262 patients. Overall, appropriateness with the 4 definitions ranged from 79% based on PI opinion to 94% based on susceptibility data. No single definition resulted in consistently high appropriate use for all target antimicrobials. For individual antimicrobials, the definitions with the highest rate of appropriate use were Clinical Pharmacology/Micromedex support (6 of 7 antimicrobials) and susceptibility data (5 of 7 antimicrobials). For specific indications, support from susceptibility data resulted in the highest rate of appropriate use (4 of 7 indications). Overall comparisons showed that appropriateness assessed by PI opinion differed significantly compared with other definitions when stratified by either target antimicrobial or indication. The significant variability in the rate of appropriate use highlights the difficulty in developing a standardized definition that can be used to benchmark judicious antimicrobial use.

Keywords. antimicrobial therapy; antimicrobial stewardship program; antimicrobial prescribing behavior; observational study.

Antimicrobials are essential for treating patients with infectious diseases; however, several recent studies have highlighted the problem of inappropriate use of antimicrobials. Antimicrobial therapy or prophylaxis has been reported to be inappropriate in >50% of hospitalized patients [1–6]. Furthermore, inappropriate use of antimicrobials increases the risk for adverse patient outcomes such as treatment failure, death, and *Clostridium difficile* infection (CDI) [5–11].

The Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) developed a comprehensive set of recommendations that includes establishment and support of antimicrobial stewardship programs in acute care hospitals to help optimize the use of antimicrobials [12]. In 2012, they joined forces with the Pediatric Infectious Diseases Society (PIDS) to extend their recommendations beyond acute care settings and into additional patient populations [13]. Given the urgent need to address the growing problem of antimicrobial resistance, the Centers for Disease Control and Prevention (CDC) has recommended that all hospitals implement an antimicrobial stewardship program and has also developed guidelines

[a]Present affiliation: Vital Care, Inc, Meridian, Mississippi.
[b]Present affiliation: Department of Pharmacy, Houston Methodist Hospital, Texas.
Correspondence: Elizabeth D. Hermsen, PharmD, MBA, BCPS-ID, Cubist Pharmaceuticals, 65 Hayden Ave, Lexington, MA 02421 (elizabeth.hermsen@cubist.com).

Clinical Infectious Diseases 2014;59(S3):S154–61

DOI: 10.1093/cid/ciu548

Table 1. Characteristics of Study Sites Selected to Assess the Definitions of Appropriateness

Characteristic	Creighton University Medical Center	University of Arkansas for Medical Sciences Medical Center	Huntsville Hospital	University of New Mexico Health Sciences Center
Institution type	Academic/university	Academic/university	Community teaching	Academic/university
Hospital system type	Single institution	Multiple institutions	Multiple institutions	Single institution
Hospital inpatient bed size, No. of beds	>250–500	>250–500	>750–1000	>500–750
Time antimicrobial stewardship program has been in place, y	<1	<1	4–6	1–3
Antimicrobial stewardship CDSS	Plan to purchase/ implement within next 12 mo	Plan to purchase/ implement within next 12 mo	Yes	No
Computerized physician order entry system	No	Yes	No	Yes
Electronic medical record system	Yes	Yes	Yes	Yes
Core antimicrobial stewardship program personnel				
ID physician + ID pharmacist[a]	Yes	Yes	Yes	No
Other	Yes[b,c]	No	Yes[c,d]	No
Core/supplemental strategies used				
Prospective audit with intervention and feedback	Yes	Yes	Yes	Yes
Formulary restriction and preauthorization	No	No	No	Yes
Education	Yes	No	Yes	Yes
Institution-specific guidelines and clinical pathways	Yes	Yes	Yes	Yes
Order forms, including computerized order algorithms/order sets	Yes	Yes	Yes	No
Streamlining or de-escalation	Yes	Yes	Yes	Yes
Dose optimization	Yes	No	Yes	Yes
IV-to-oral conversion	Yes	Yes	Yes	Yes
Antimicrobial cycling	No	No	No	No

Abbreviations: CDSS, clinical decision support system; ID, infectious disease; IV, intravenous; MAD-ID, Making a Difference in Infectious Diseases; SIDP, Society of Infectious Diseases Pharmacists.

[a] ID PharmD (includes residency/fellowship trained in ID, MAD-ID, or SIDP; MAD-ID and SIDP are both certificate programs).

[b] Non-ID pharmacist.

[c] Clinical microbiologist.

[d] Information system/data specialist.

and other tools to assist institutions with antimicrobial stewardship [14].

Antimicrobial stewardship is a rational, systematic approach to improving appropriate use of antimicrobials to achieve optimal outcomes [12, 15]. However, standardized definitions of appropriate and inappropriate therapy are lacking, as are metrics and drivers of such use [13]. Studies reported in the literature have used a variety of definitions to assess appropriate use. Most commonly, *appropriate therapy* is defined as selection of an antimicrobial that has in vitro activity against the isolated pathogen [7–9, 16–18]. Another definition of appropriateness in the literature is use consistent with current practice guidelines or accepted norms for the site of infection [9, 18, 19] or in agreement with institutional protocols [8, 20]. In certain studies, the appropriateness of prescribing is evaluated by infectious disease specialists [5, 6, 19, 21, 22]. Because a key goal for an antimicrobial stewardship program is to facilitate judicious antimicrobial use and because no consensus exists regarding how to define this, we sought to compare 4 definitions of appropriateness in a multicenter, observational study.

METHODS

Study Design

This was an observational, retrospective, cohort study conducted at 4 sites in the United States to assist institutions with monitoring and reporting on the use of selected antimicrobials for treatment of suspected or documented infections caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and *Pseudomonas aeruginosa* (Table 1). Between 1 January and 31 December 2011, consecutive patients treated with the selected antimicrobials were screened for

Table 2. Current Definitions of Appropriate Use of Antimicrobial Therapy

1. Study site–specific definition (Supplementary Appendix)
2. Supported by in vitro susceptibility data
3. Antimicrobial used for indication supported by Clinical Pharmacology (Elsevier/Gold Standard, Tampa, Florida)[a] or Micromedex (Truven Health Analytics, Ann Arbor, Michigan)[a] (ie, proven clinical data with clinical trial/literature support, including uses that are not approved indications by the US Food and Drug Administration)
4. Opinion of the principal investigator based on a modified version of criteria by Kunin et al [23] (categories I and II were considered appropriate, whereas III–V were considered inappropriate) I—Agree with use of antimicrobial therapy and the drug regimen is appropriate II—Agree with use of antimicrobial therapy and the drug regimen is probably appropriate III—Agree with use of antimicrobial therapy, but a different antimicrobial is preferred IV—Agree with use of antimicrobial therapy, but a different mode of therapy is preferred V—Disagree with use of antimicrobial therapy, administration is unjustified

[a] Electronic drug information resources.

eligibility based on a systematic review of medical records. The selected antimicrobials were targeted based on their in vitro activity vs many of the ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* species) pathogens and included cefepime, ceftaroline, ceftazidime, colistimethate (intravenous only), daptomycin, doripenem, imipenem, linezolid, meropenem, piperacillin/tazobactam, polymyxin B (intravenous only), tigecycline, and vancomycin (intravenous only). Each site was to enroll a minimum of 25 patients who received 1 of the selected antimicrobials, with the exception of ceftaroline, polymyxin (colistimethate or polymyxin B; intravenous only), and tigecycline, for a total of 150 patients. Sites were to enroll all patients treated with ceftaroline, a polymyxin, or tigecycline unless they had >25 patients for each of these drugs, in which case only 25 patients were necessary for each. A waiver of informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization was approved from the institutional review board at each study site.

Study Population

To be eligible, the patient must have received a target antimicrobial for ≥3 days for treatment of a suspected or documented infection within the 12-month study period and have completed therapy in the 2011 calendar year. Patients receiving any target antimicrobial as part of a controlled clinical trial were excluded. A patient could be enrolled only once for a given antimicrobial. To improve the impartiality of patient selection, each site was to select and report on the first 6 or 7 patients completing therapy during four 3-month periods in 2011, with the next patient in sequence being chosen if the previous patient was ineligible. Principal investigators were not prescribers.

Table 3. Demographic and Clinical Characteristics at Admission

Characteristic	No. of Patients[a] (N = 262)
Age at admission, y	
Mean (SD)	57.9 (17.1)
Median (min, max)	60.5 (15, 89)
Male sex	141 (53.8)
Race/ethnicity	
White	208 (79.4)
Black	48 (18.3)
Hispanic	3 (1.1)
American Indian/Alaska Native	1 (0.4)
Other	2 (0.8)
Location before admission[a]	
Home	199 (76.0)
Long-term-care facility	30 (11.5)
Hospital	24 (9.2)
Rehabilitation facility	5 (1.9)
Other	4 (1.5)
Antimicrobial therapy within 30 d preceding antimicrobial initiation	123 (46.9)
Hospitalization within 30 d preceding antimicrobial initiation	97 (37.0)
Serum creatinine at start of target antimicrobial treatment, mg/dL, mean (SD)	1.4 (1.1)
Estimated creatinine clearance, mL/min, mean (SD)	76.0 (53.1)
Dialysis at initiation of antimicrobial therapy	22 (8.4)
Immunocompromised state[b]	37 (14.1)
Target antimicrobial[a]	
Cefepime	55 (21.0)
Ceftaroline	21 (8.0)
Daptomycin	52 (19.8)
Linezolid	50 (19.1)
Piperacillin-tazobactam	29 (11.1)
Tigecycline	25 (9.5)
Vancomycin (IV only)	21 (8.0)
Other (doripenem, imipenem, meropenem, ceftazidime, colistin/colistimethate [IV only], polymyxin B [IV only])	9 (3.4)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: IV, intravenous; SD, standard deviation.

[a] Because of rounding percentages might not add up to or might exceed 100%.

[b] Defined as human immunodeficiency virus infection, neutropenia, or long-term corticosteroid use.

Data Collected

We extracted 4 categories of data from each patient's record: (1) patient characteristics: demographics, hospital and intensive care unit admission and discharge dates, and baseline serum

Table 4. Appropriateness of Treatment by Target Antimicrobial and Definition[a]

Appropriateness Definition	No. (%) Receiving Appropriate Therapy							
	Cefepime (n = 55)	Ceftaroline (n = 21)	Daptomycin (n = 52)	Linezolid (n = 50)	Piperacillin-Tazobactam (n = 29)	Tigecycline (n = 25)	Vancomycin (n = 21)	Overall (N = 262)
Site definition	54 (98.2)	21 (100.0)	46 (88.5)	27 (54.0)	29 (100.0)	25 (100.0)	21 (100.0)	231 (88.2)
Susceptibility data support[b]	39/43 (90.7)	6/6 (100.0)	24/26 (92.3)	12/15 (80.0)	26/26 (100.0)	10/10 (100.0)	21/21 (100.0)	145/154 (94.2)
Clinical Pharmacology/ Micromedex[c] support	55 (100.0)	21 (100.0)	31 (59.6)	44 (88.0)	29 (100.0)	25 (100.0)	21 (100.0)	233 (88.9)
PI opinion (Kunin et al [23] categories 1 and 2)	46 (83.6)	21(100.0)	44 (84.6)	19 (38.0)	28 (96.6)	25 (100.0)	21 (100.0)	207 (79.0)

Abbreviation: PI, principal investigator.

[a] Data are shown only for antimicrobials received by ≥20 patients, with the exception of the overall column, which includes all patients: doripenem (n = 1), imipenem (n = 0), meropenem (n = 2), ceftazidime (n = 0), colistin/colistimethate (n = 6) .

[b] Number in individual cells denotes number of patients with susceptibility data supporting the use of the target antimicrobial, with the total number of patients with susceptibility data available as the denominator.

[c] Clinical Pharmacology by Elsevier/Gold Standard, Tampa, Florida; Micromedex by Truven Health Analytics, Ann Arbor, Michigan.

creatinine; (2) significant medical history: location before hospitalization, receipt of antimicrobial therapy within 30 days before target antimicrobial initiation, previous hospitalization, receipt of dialysis at initiation of antimicrobial therapy, and presence of an immunocompromised state (neutropenia, corticosteroid use, or infection with human immunodeficiency virus); (3) antimicrobial treatment: indication and dosing regimen for the target antimicrobial, use of other antimicrobials, and appropriateness of antimicrobial therapy; and (4) microbiology: culture and susceptibility data relevant to the target antimicrobial indication.

Primary Endpoint

We used 4 definitions for appropriateness of antimicrobial therapy (Table 2): a study site–specific definition (Supplementary Appendix) and 3 protocol-specific definitions [23]. Each definition of appropriate therapy was assessed separately by 1 individual at each study site.

Statistical Analyses

The primary analysis population was the all-treated population, which included all patients enrolled in the study. Data for appropriate and inappropriate therapy were summarized by numbers and percentages for each antimicrobial and indication according to each definition. Appropriateness of treatment was stratified by antimicrobial and indication. Incidence rates of appropriateness according to the various definitions were compared with the χ^2 test or Fisher exact test, and comparisons were made only for groups with at least 20 patients. Statistical analyses were performed using SAS version 9.2 software (SAS Institute, Cary, North Carolina). A P value <.05 indicated statistical significance.

RESULTS

Patient Characteristics

Overall, data were collected for 262 patients: 139 (53%) from Huntsville Hospital, 81 (31%) from the University of Arkansas for Medical Sciences Medical Center, 39 (15%) from Creighton University Medical Center, and 3 (1%) from University of New Mexico Hospital. Mean ± SD patient age was 57.9 ± 17.1 years, and most were male (53.8%) and white (79.4%) (Table 3). Approximately 50% of patients had received antimicrobial therapy and more than one-third had been hospitalized in the 30 days preceding initiation of the target antimicrobial. The most common target antimicrobials included were cefepime (21%), daptomycin (19.8%), and linezolid (19.1%) (Table 3). Overall appropriateness with the 4 definitions ranged between 79% based on principal investigator (PI) opinion and 94% based on susceptibility data (Tables 4 and 5).

Appropriateness of Treatment According to Target Antimicrobial

No single definition consistently resulted in appropriate use when applied across all targeted antimicrobials (Table 4). For individual antimicrobials, the definitions resulting in the highest rate of appropriate use were Clinical Pharmacology (Elsevier/Gold Standard, Tampa, Florida) or Micromedex (Truven

Table 5. Appropriateness of Treatment by Indication and Definition[a]

Appropriateness Definition	No. (%) Receiving Appropriate Therapy							
	Bacteremia (n = 44)	Nosocomial Pneumonia (n = 42)	Bone Infections/ Osteomyelitis (n = 25)	Skin and Skin Structure Infection (n = 88)	Surgical Site Infection (n = 28)	Urinary Tract Infection (n = 37)	Intra-abdominal Infection (n = 29)	Overall (N = 262)
Site definition	43 (97.7)	30 (71.4)	23 (92.0)	87 (98.9)	25 (89.3)	30 (81.1)	24 (82.8)	231 (88.2)
Susceptibility data support[b]	39/39 (100.0)	18/22 (81.8)	13/14 (92.9)	42/43 (97.7)	18/19 (94.7)	30/30 (100.0)	15/15 (100.0)	145/154 (94.1)
Clinical Pharmacology/ Micromedex[c] support	33 (75.0)	42 (100.0)	22 (88.0)	87 (98.9)	26 (92.9)	32 (86.5)	24 (82.8)	233 (88.9)
PI opinion (Kunin et al [23] categories 1 and 2)	39 (88.6)	21(50.0)	22 (88.0)	86 (97.7)	23 (100.0)	24 (64.9)	24 (82.8)	207 (79.0)

Abbreviation: PI, principal investigator.

[a] Data are shown only for indications present in ≥20 patients, with the exception of the overall column, which includes all patients: community-acquired pneumonia (n = 10), endocarditis (n = 4), lower respiratory infection (other than pneumonia) (n = 4), septic arthritis (n = 4).

[b] Number in individual cells denotes number of patients with susceptibility data supporting the use of the target antimicrobial, with the total number of patients with susceptibility data available as the denominator.

[c] Clinical Pharmacology by Elsevier/Gold Standard, Tampa, Florida; Micromedex by Truven Health Analytics, Ann Arbor, Michigan.

Health Analytics, Ann Arbor, Michigan) support (6 of 7 antimicrobials) and susceptibility data support (5 of 7 antimicrobials). The greatest variation in appropriate use according to definition was observed with daptomycin and linezolid. Appropriate use for daptomycin ranged from 59.6% for Clinical Pharmacology/Micromedex support to 92.3% for susceptibility data support, and for linezolid, from 38% for PI opinion to 88% for Clinical Pharmacology/Micromedex support.

Overall comparisons show that appropriateness assessed by PI opinion differed significantly compared with other

Table 6. Pairwise Comparison of Definitions of Appropriateness by Target Antimicrobial[a]

Comparison (*P* Values*)	Cefepime (n = 55)	Ceftaroline (n = 21)	Daptomycin (n = 52)	Linezolid (n = 50)	Piperacillin-Tazobactam (n = 29)	Tigecycline (n = 25)	Vancomycin (n = 21)	Overall (N = 262)
Site definition vs susceptibility data	.1653	NA	.7118	.0714	NA	NA	NA	.0455
Site definition vs Clinical Pharmacology/ Micromedex[b] support	1.0000	NA	.0008	.0002	NA	NA	NA	.7838
Site definition vs PI opinion	.0080	NA	.5656	.1085	1.0000	NA	NA	.0046
Susceptibility data vs Clinical Pharmacology/ Micromedex support	.0342	NA	.0028	.4200	NA	NA	NA	.0741
Susceptibility data vs PI opinion	.3065	NA	.4817	.0043	1.0000	NA	NA	<.0001
Clinical Pharmacology/ Micromedex support vs PI opinion	.0027	NA	.0045	<.0001	1.0000	NA	NA	.0020

Abbreviations: NA, insufficient data to conduct test of agreement; PI, principal investigator.

[a] Data are shown only for antimicrobials received by ≥20 patients, with the exception of the overall column, which includes all patients.

[b] Clinical Pharmacology by Elsevier/Gold Standard, Tampa, Florida; Micromedex by Truven Health Analytics, Ann Arbor, Michigan.

* *P* values are based on χ^2 test or Fisher exact test as appropriate.

Table 7. Pairwise Comparison of Definitions of Appropriate Treatment by Indication[a]

Appropriateness Definition (*P* Values*)	Bacteremia (n = 44)	Nosocomial Pneumonia (n = 42)	Bone Infections/ Osteomyelitis (n = 25)	Skin and Skin Structure Infection (n = 88)	Surgical Site Infection (n = 28)	Urinary Tract Infection (n = 37)	Intra-abdominal Infection (n = 29)	Overall (N = 262)
Site definition vs susceptibility data	1.0000	.3619	1.0000	.5504	.6376	.0142	.1486	.0455
Site definition vs Clinical Pharmacology/ Micromedex[b] support	.0019	.0002	1.0000	1.0000	1.0000	.5282	1.0000	.7838
Site definition vs PI opinion	.2024	.0444	1.0000	1.0000	.7049	.1163	1.0000	.0046
Susceptibility data vs Clinical Pharmacology/ Micromedex support	.0008	.0115	1.0000	.5504	1.0000	.0599	.1486	.0741
Susceptibility data vs PI opinion	.0572	.0132	1.0000	1.0000	.3783	.0003	.1486	<.0001
Clinical Pharmacology/ Micromedex support vs PI opinion	.0973	<.0001	1.0000	1.0000	.4216	.0302	1.0000	.0020

Abbreviation: PI, principal investigator.

[a] Data are shown only for antimicrobials received by ≥20 patients, with the exception of the overall column, which includes all patients.

[b] Clinical Pharmacology by Elsevier/Gold Standard, Tampa, Florida; Micromedex by Truven Health Analytics, Ann Arbor, Michigan.

* *P* values are based on χ^2 test or Fisher exact test as appropriate.

definitions (Table 6). Where statistically significant differences existed, the direction of the difference was not consistent. For example, evaluation of daptomycin and linezolid showed that the appropriateness of daptomycin, as defined by PI opinion or the study site definition, was higher than that defined by Clinical Pharmacology/Micromedex, whereas the reverse was true for linezolid (ie, appropriateness as defined by PI opinion or the study site definition was lower than that defined by Clinical Pharmacology/Micromedex).

Appropriateness of Treatment According to Indication

No single definition consistently resulted in appropriate use when applied across all indications (Table 5). For individual indications, the definition with the highest rate of appropriate use was susceptibility data support (4 of 7 indications). Nosocomial pneumonia and urinary tract infection had the greatest variation across the definitions for appropriate use. The rate of appropriateness ranged from 50% for PI opinion to 100% for Clinical Pharmacology/Micromedex support for nosocomial pneumonia and from 64.9% for PI opinion to 100% for susceptibility data support for urinary tract infection.

Overall comparisons show that appropriateness assessed by PI opinion differed significantly compared with all other definitions (Table 7). The overall study site definition differed significantly from susceptibility data. This was primarily because of a lower rate of appropriateness comparing study site definition with susceptibility data support for urinary tract infection (Table 7). Where statistically significant differences exist for PI opinion, the direction of the difference is consistent: appropriateness as defined by PI opinion is lower than with the other definitions.

DISCUSSION

Cornerstone goals of an antimicrobial stewardship program are to improve and measure the appropriate use of antimicrobial agents by promoting the selection of an optimal antimicrobial regimen, including indication, dosing, duration of therapy, and route of administration [13]. For antimicrobial use to improve, prescribers must be provided with feedback about inappropriate use and educated on strategies to curb antimicrobial resistance. Currently, benchmarks on antimicrobial use in US institutions, such as defined daily dose and days of therapy, focus on overall antimicrobial use and not on whether that use is appropriate. Because antimicrobial use will never be eliminated, assessment of appropriateness of use should be required as a benchmark. Understanding the level of appropriateness relative to use will allow antimicrobial stewardship program personnel to recognize the threshold at which any further reduction in use is unwarranted (ie, all use or a high proportion of use is both appropriate and judicious). Understanding appropriateness of therapy would help antimicrobial stewardship programs target

efforts toward reducing inappropriate or unnecessary use, and facilitate appropriate use in an effort to improve patient outcomes.

A key element for encouraging appropriate use in hospitals is defining what is considered appropriate and remaining consistent with that interpretation. A standardized definition of appropriate antimicrobial use is lacking, as are clear and unambiguous measures of such use [13]. As discussed previously, criteria for appropriate antimicrobial use vary widely among studies [5–9, 16–22].

Our study compared the proportion of antimicrobial orders considered appropriate according to separate definitions and found significant disparity among definitions, particularly between PI opinion and other standard definitions of appropriate use. Differences were found whether definitions were compared by drug or by indication. The results underscore the difficulty of assessing appropriateness based on a rote definition without clinical interpretation, and this assessment is far easier when done in hindsight. For example, support from susceptibility data provided the highest rate of appropriate use in the overall population, but there were significant differences when compared with PI opinion for linezolid, nosocomial pneumonia, and urinary tract infection, with appropriateness according to susceptibility data being higher in all cases. Interestingly, although our patient population was at increased risk for adverse consequences of antimicrobial use (approximately 50% of the patients had recent exposure to antimicrobials and more than one-third had been recently hospitalized) and should have been scrutinized for appropriate antimicrobial use, the divergence in appropriateness was striking.

A reason for this disconnect might be that standard definitions do not take into account other factors that should be considered when determining appropriate therapy. In clinical practice, appropriateness changes on a daily basis as more information about the patient/infection becomes available. Clinical judgment is often needed to ascertain the most appropriate drug for individual patients with complicated clinical scenarios. Patients might have physiologic changes that alter antimicrobial pharmacokinetics and pharmacodynamics, and, hence, decisions made by investigators might not agree with guidelines or susceptibility data [24, 25]. In addition, previous antimicrobial history and response have an impact on what might be considered appropriate; sometimes a choice deemed inappropriate by a single criterion is ultimately the best choice for a patient at the time of therapy selection. The site of infection also guides antimicrobial choice because the concentration at the infection site is an important determinant of the clinical effectiveness of a drug [26].

The CDC has recognized the need to standardize the assessment of appropriate antimicrobial prescription and is developing tools to assist clinicians. Worksheets have been developed to assess appropriateness of antimicrobial use for various indications, including community-acquired pneumonia, urinary tract infection, resistant gram-positive infections, and inpatient use [14]. These worksheets contain questions related to underlying comorbidity, documented signs and symptoms of infection, whether empiric antimicrobial therapy was administered, tests performed to identify and determine the susceptibility of the causative pathogen, and total duration of antimicrobial therapy. No overall score or assessment of appropriateness is indicated on the worksheets, but the worksheets could allow for a similar assessment for our study with regard to appropriateness according to study site definition or susceptibility data.

Our study has limitations, which are noted. This was a retrospective study, with a small sample size in subgroups. Because of the limited data collection period and lack of a predefined order to collect data for each of the antimicrobials, the data might be skewed within each institution based on the order in which the investigator collected data (eg, a site might have chosen to start with vancomycin and piperacillin/tazobactam but was not able to collect data for the other drugs within the limited data collection time frame). Although each definition was assessed separately, the assessments were not blinded and, therefore, had the potential for bias. However, assessments at each institution were performed by a single individual, which should have provided consistency in assessments across the various drugs and indications within each institution. Yet, the retrospective nature of our analysis reflects real-world data as we relied on the provider's diagnosis of infections and use of antibiotics. Because PI opinion is subjective and shaped not only by an individual patient's clinical scenario, but also by outside factors such as training, previous experience, and hospital formulary, it is likely that the opinions of PIs varied widely across institutions. The selection of Clinical Pharmacology and Micromedex as references for one of the standard definitions of appropriateness vs other references such as the *Sanford Guide to Antimicrobial Therapy* (Antimicrobial Therapy, Sperryville, Virginia), UpToDate (Wolters Kluwer Health, Philadelphia, Pennsylvania), or IDSA guidelines was arbitrary; however, all these references provide widely accepted uses for antimicrobials based on available data. Last, susceptibility data were missing for several patients, likely attributable to antimicrobials being initiated empirically with no subsequent positive cultures.

In summary, our multicenter study showed significant differences in the proportion of antimicrobial prescriptions considered appropriate depending on the definition of appropriate use. These findings underscore the difficulty in developing a standardized definition that can be used within and across institutions to assess antimicrobial appropriateness. The study also highlights the discrepancies encountered between clinical judgment (PI opinion), which is used on a daily basis to assess antimicrobial appropriateness in practice, and standard, objective definitions such as susceptibility data. A recommendation

for the ideal definition cannot be made from this study because no single definition encompassed appropriate use for all antimicrobials and indications evaluated. Future research should investigate the use of combined definitions of appropriateness, the correlation between various definitions of appropriateness and clinical outcomes, and the identification and application of surrogate markers of appropriateness.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. Writing and editorial support was provided by ApotheCom ScopeMedical (Yardley, Pennsylvania) and funded by Cubist Pharmaceuticals.

Supplement sponsorship. This article appears as part of a supplement titled "Antimicrobial Stewardship: Patients Over Process," sponsored by Cubist Pharmaceuticals.

Potential conflicts of interest. D. D. D., E. D. H., K. C. L., and T. J. C. are all employees of Cubist Pharmaceuticals and own stock. C. J. D., K. L., E. H. E., and R.-C. M. received consulting fees/honorarium from Cubist Pharmaceuticals and support for travel to meetings for the study from Cubist Pharmaceuticals; R.-C. M. has given lectures for Cubist Pharmaceuticals on topics unrelated to this article for which her institution received a fee; and P. M. M. was employed by the Massachusetts College of Pharmacy and Health Sciences as a postdoctoral fellow with Cubist Pharmaceuticals (fellow stipend funded by Cubist Pharmaceuticals) from July 2011 to June 2013, and is a stockholder of Cubist Pharmaceuticals.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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